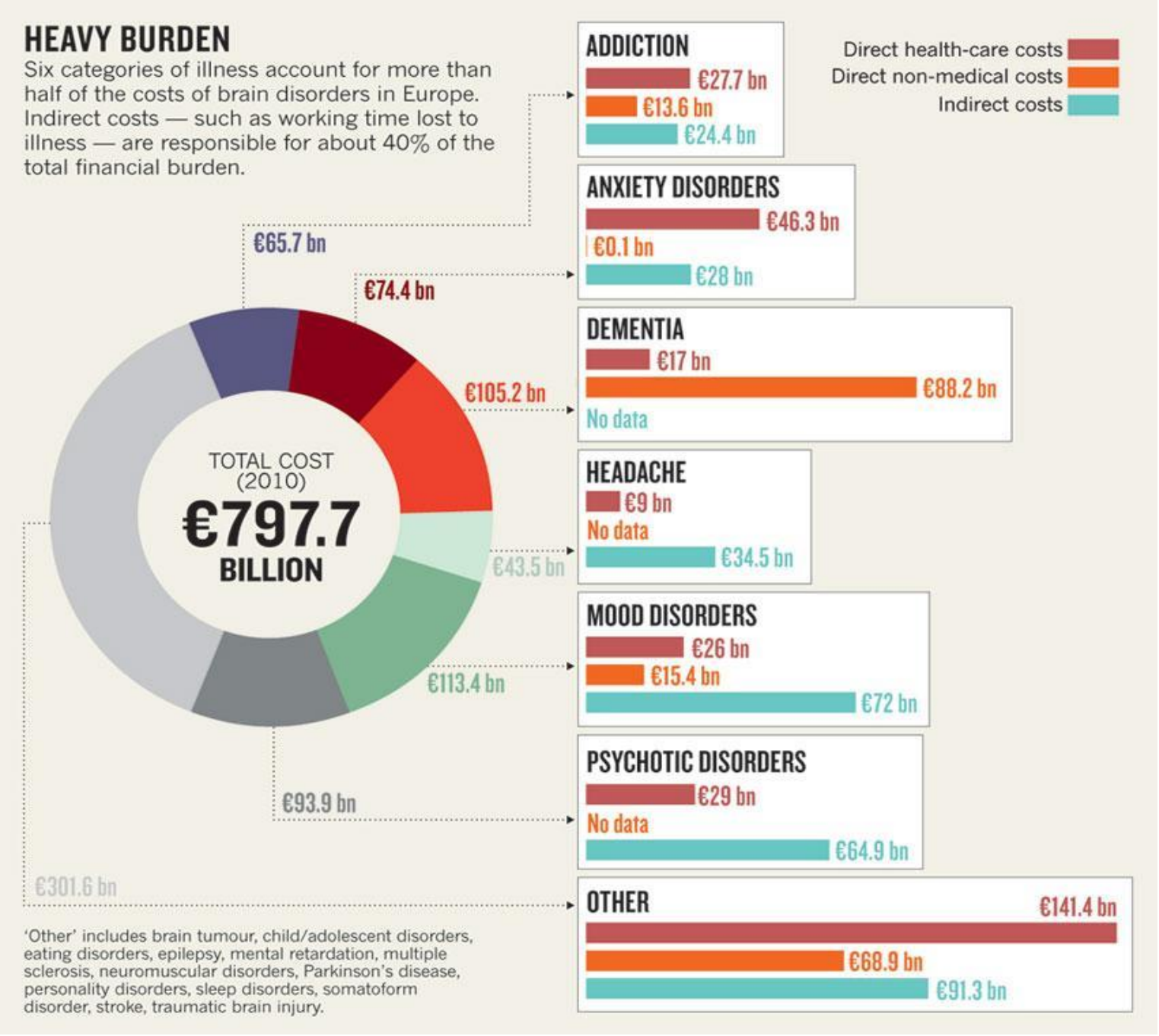
Psych 3102
Introduction to Behavioral Genetics

Lecture 21

Genetics of mental disorders

Adult psychopathology



Europe
- $1 trillion/year

More than cancer, cardiovascular disease, diabetes combined

Mood disorders most costly, followed by dementia

37%=direct costs (drugs,doctors, Hospitals)
23%=direct non-medical (social services, care, homes)
40%=indirect (lost productivity, early retirement)

Costs will be much higher in US

High incidence of serious psychological episodes

- account for 1/3 of disability worldwide
- USA 50% report at least one episode/lifetime
  30% report an episode within the last year

Adult psychopathologies studied in behavior genetics:

schizophrenia

affective/mood disorders depression bipolar disorder

substance abuse disorders alcoholism

personality disorders anti-social personality disorder

Childhood

autism/autistic spectrum disorders

ADHD

conduct disorder

Limitations of the current diagnoses

1. mental illness is classified into a series of discrete disorders

no measure of severity disorder is either present or absent

cognitively, each disorder was originally seen as resulting from single core deficit caused by specific genetic or environmental risk factor (single-deficit theory)
challenged by comorbidity observed

2. each symptom used to diagnose the disorder is equally weighted

each may not be equally important the 'disorder' itself may not even exist

different symptoms in those with same disorder make locating genes difficult

3. multiple diagnoses are possible in same person (comorbidity)

level of comorbidity is high – people having one disorder are likely to have another as well

network modeling: ½ DSMIV symptoms are connected, symptoms can be clustered but path length is short, distances between disorders can predict measured comorbidity rates

4. Current organization - multiple ‘axes’ :

not based on information from genetic studies or even actual phenotypic structure

Axis I clinical syndromes & disorders eg depression

Axis II personality disorders & mental retardation stable, long-standing

Axis III general medical conditions that effect mental health eg syphilis, diabetes

Axis IV psychosocial problems eg job loss that effects mental health

Axis V global assessment of functioning overall rating of social, occupational & psychological abilities

little distinction between some disorders in different axes (eg OCD & OCPD)

alternative model based on phenotypic structure often used in behavior genetics – hopefully reflected in DSM-V

Krueger, 1999 Arch.Gen Psych, 56, 924

Review of definitions:

- prevalence measure of the occurrence of a disorder in the population studied
- risk measure of the occurrence of a disorder in a proband's family
- proband person presenting the disorder
- concordance measure of how often related pairs (usually twins) in the sample both show the disorder
- correlation a standardized measure of shared variance between 2 samples, used as statistical measure of resemblance between relatives
- liability-threshold model hypothesis explaining a disorder as the phenotypic expression at one extreme end of a normal distribution of variation for the trait (threshold is fixed)
- comorbidity co-occurrence of 2 or more disorders in the same person
- latent trait analysis multivariate factor analysis used to detect evidence for a common factor underlying comorbidity
- endophenotype (biomarker) an easily-measured variable that is part of a more complex phenotype

may predict risk for a disorder may help in the diagnosis of a disorder

Schizophrenia (SCZ)

- long-term psychotic disorder (symptoms have to occur for 6 months)

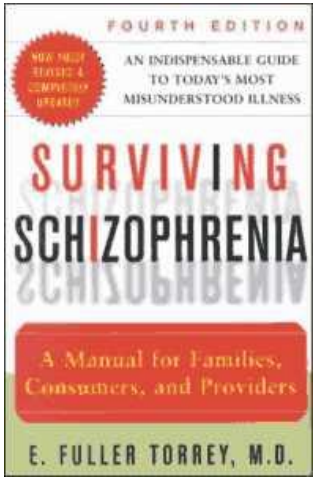
'active' symptoms

- delusions, hallucinations (especially auditory)
- gross impairment in reality-testing, loss of ego boundaries
- disorganized speech, behavior

- affective flattening, less goal-oriented behavior (avolition)

'passive' symptoms worse level = catatonia

- marked social, occupational dysfunction
- 2-3 fold increased risk of dying, life expectancy decreased by 12-15 years



Onset: late adolescence, early adulthood (later in females)
prognosis worse with earlier onset
episodic but lasts a lifetime

Prevalence: 1% worldwide, lifetime
across sites/populations point prevalence varies, as does incidence

Causes

- developmental neurological disorder with strong genetic component
- a pathway disease – a biological pathway is altered
- neurological differences seen in SCZ brains:
  - likely present at birth to some extent - experiences not causal on own
  - reduced brain volume, cell size, spine density, abnormal neural distribution in prefrontal cortex & hippocampus
  - dopaminergic, glutamatergic, GABAergic activity implicated

Treatments

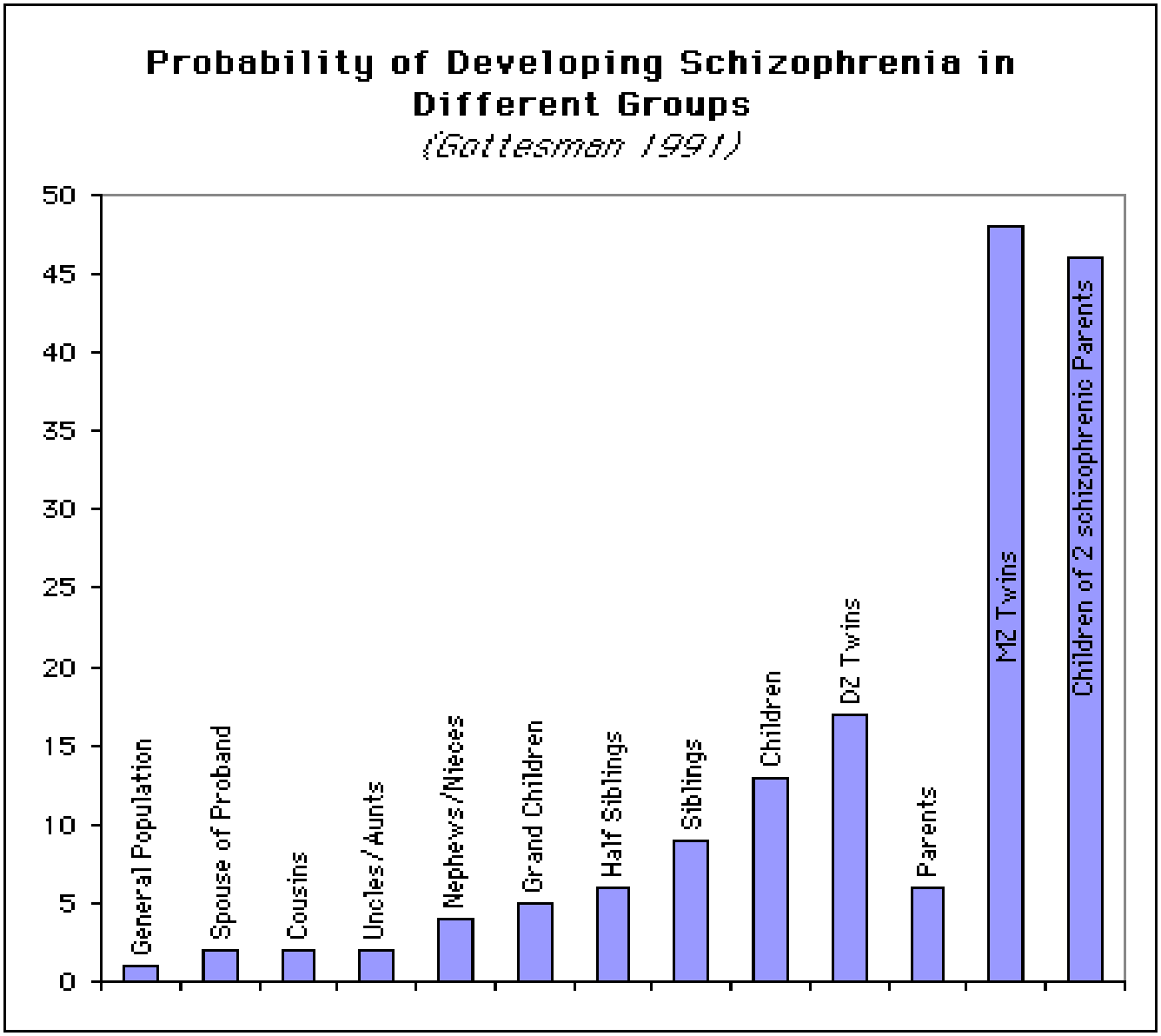
antipsychotic (neuroleptic) drugs, behavioral therapy, support systems now manage most symptoms

Drug treatments currently aimed mostly at dopamine system

'hyperactive' brain component

Clozapine , Thorazine etc help by reducing dopamine levels

Schizophrenia shows familiality



Median risk estimates for general population and for relatives of schizophrenic index cases

General population (prevalence)	1%
Spouses	2%
MZ twins	48%
DZ twins	17%
First degree relatives of schizophrenics	
parents	6%
siblings	9%
children	13%
adopted-away children	11%
Second degree relatives	3.3%
Third degree relatives	2.4%

14 family studies, 8000 schizophrenics + family members

Evidence for genetic influence?

Why is risk lower for parents of schizophrenics compared to other 1^{o} relatives?

Why is spousal risk double prevalence?

Twin and adoption studies

- 4 early twin studies: concordances MZ = 48%
  DZ = 17%

- heritability 80% (95%confidence interval, 73-90%)
  - based on meta-analysis of 12 twin studies and liability threshold model
    Sullivan, Kendler, Neale (2003) Arch. Gen.Psychiatry
    quantitative meta-analysis removes biases possibly present in single studies
    improves statistical power to detect subtle influences missing in smaller studies
  - additive genetic effects
  - evidence for small shared e of 11% (3-19% 95% conf. interval)
    portion of this could be due to assortative mating

- adoption studies:
  adopted-apart MZ twims 64% concordance (14 twin pairs)
  adopted-apart sibs risk = 11% (same as reared together)
  confirms shared environment seems to be relatively unimportant

- schizo-affective disorder and schizoid personality disorder also run in some families of schizophrenics

Environmental components

- **Shared e component**
  likely to work early in development when environment is most similar
  prenatal at birth shortly after birth

- little evidence of pre-natal effects as sole cause
  - risk to children is similar whether Mom or Dad had SZ,
  - half-sibling data confirm this

- **G x E**
  - at risk offspring had higher risk if adopted into poor-functioning homes

- **Non-shared environment** or stochastic events are important

birth complications neurological abnormalities
attention problems as children prenatal viral infections
} all more common in MZ twin with sz

Morbidity risk (MR%) of schizophrenic symptoms in offspring of schizophrenic twin pairs

Gottesman (1989) Danish twin registry

co-twin control method - study of discordant twins used to seek out causal environmental events

		N	MR%(offspring)	
MZ	Schizophrenic twins	47	16.8	first degree relative risk
	'Normal' co-twins	24	17.4	
DZ	Schizophrenic twins	27	17.4	
	'Normal' co-twins	52	2.1	second degree relative risk

offspring of non-SCZ MZ co-twin were as likely to develop SCZ as offspring of SCZ MZ co-twin

indicates non-penetrance of scz risk alleles – unexpressed genotypes are passed on

This image is of 28-year-old identical twins, one with schizophrenia and the other well. It therefore clearly illustrates two points: (1) schizophrenia is a brain disease with measurable structural and functional abnormalities in the brain; and (2) it is not a purely genetic disease, and other biological factors play a role in its etiology.

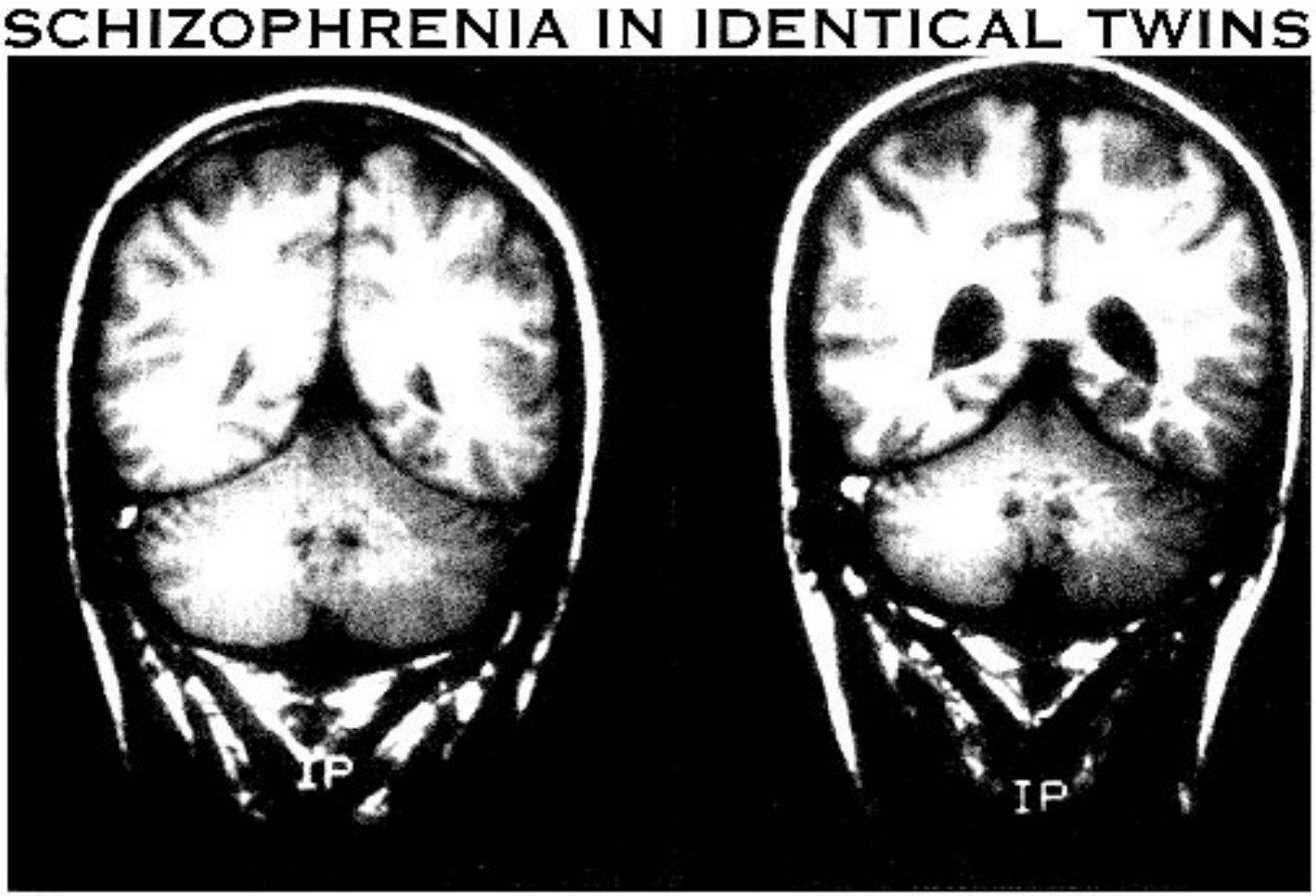


Photo courtesy of Drs. E. Fuller Torrey and Daniel Weinberger.

MRI scans of 28-year-old male identical twins showing the enlarged brain ventricles in the twin with schizophrenia (right) compared to his well brother (left).

Defining schizophrenia

now considered a heterogeneous set of disorders

1. 'classical' subtypes:
   - catatonic (passive, motor symptoms)
   - paranoid (active, psychotic symptoms)

   not supported by evidence from genetic studies
   - particular subtype does NOT run in families
   - overall tendency does

2. more severe forms are more heritable:
   - Type I best prognosis, active symptoms only (hallucinations), responds well to drug treatment, less severe, less heritable
   - Type II worse prognosis, more severe, active and passive symptoms (withdrawal) , less treatable
     higher rate of affected family members, more heritable

- fits well with liability-threshold model for the disorder

Biological basis - abnormal brain development

1. hyperactiviity of brain dopaminergic systems

- high doses of amphetamine in normal brain produces some scz symptoms
- typical anti-psychotics (thorazine, clozapine) act by reducing dopamine

overactivity of protein kinase C may be involved – mild stress raises activity -> onset/worsening of symptoms

- supported by mouse model with impaired attention induced by amphetamine, typical anti-psychotics reduce symptoms

2. serotonin system

- serotonin agonists also produce some symptoms

3. glutamate system (memory, learning, perception)

- ketamine, PCP block glutamate release -> many SCZ symptoms
- ketamine response may predict whether active or passive symptoms occur in individual (Nature Neuroscience, 2008, 28, 6295)

Other impairments

cognitive deficits in information-processing and stimulus-filtering (do not allow filtering of most sensory & cognitive stimuli)

- sensorimotor-gating deficits eg prepulse inhibition is reduced or absent in scz

social-interaction impairments

- using Schizotypy Symptom Q. (SIS)

40 min interviews, social isolation and guardedness significantly higher in patients and relatives

Prevalence of hallucination probably much higher than previously thought – some measures put it at 10-25% magical thinking

- normal distribution of symptoms?

Predicting liability and finding genes

- early diagnosis, predicting those at greatest risk seems important: treatment of early signs prior to first episode may result in better prognosis (Erlenmeyer-Kimling et al, 2001)
- finding reliable predictors will also aid in the search for genes
- locating liability genes will further aid diagnosis and treatment

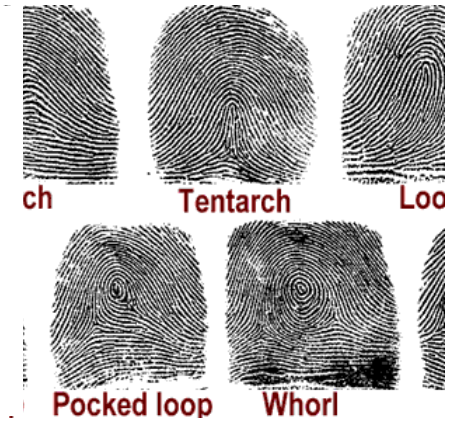
Endophenotypes – behavioral 'markers' that predict liability:

1.Neurobiological signs

poor tandem walk

poor finger/thumb opposition

dermatoglyphic asymmetry differences



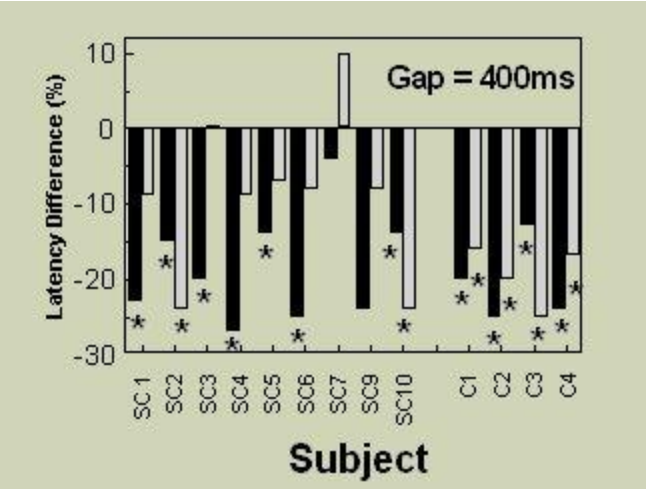
2.Childhood cognitive tests -

need all 3 for best prediction

- poor attention
- poor verbal working memory
- poor gross motor skills

smooth pursuit eye tracking (SC= scz, C=control)

3. More promising endophenotypes:



smooth-pursuit eye tracking

poor, jerky in Type II SCZ + deficits in relatives
reflects impaired spatial working memory, increased reaction time

prepulse inhibition – reduced or absent

P50 auditory ERP, sensory gating task

measures attention & vigilance, deficits seen in scz patients, family members
gene on chr 15 mouse model α7 nicotinic receptor gene promotor variants

prefrontal dysfunction indicated by Stroop task (color-naming) & fMRI

also found in unaffected relatives

California Verbal Learning Task hi error rate for perseveration

cortical mapping – differences revealed by neuroimaging, reduced frontal gray matter, hippocampal deficits

Specific genetic and environmental risk factors for schizophrenia

all causative factors must be common and global

previous candidates not likely eg deviant parenting, childhood traumatic events

Environmental factors

pregnancy complications maternal-fetal Rh blood group incompatibility

viral infections *in utero* birth complications low birthweight

season of birth likely not causal without genetic risk

GxE interactions

E seems non-specific

- any kind of stress during development + susceptibility genotypes

Other

age of father – 26-27% of SCZ patients have older fathers (+45 years old)

age 45-49 x2 risk age 50 x3 risk compared to father age 25

age of Mom does not change risk

onset of puberty – start of some prodromal symptoms

Genetic risk factors

- highly polygenic
- no Mendelian subforms identified
- each gene variant only has subtle effects, possibly by making pathway more vulnerable to environmental insults

- to identify pathway involved, 50,000 cases and another 50,000 controls would provide enough power

- hope is that pathway could be modified, development normalized

- Why does scz have such a high prevalence despite reducing fitness?

de novo mutation may be important – will be discovered when sequencing more commonly used, may account for many sporadic cases

pleiotropy of risk alleles?

High penetrance rare copy number variants (CNVs):

1q 16q 15q del22q

- none are fully penetrant – risk factors, present in some without SCZ
- nearly all are non-specific - risk for SCZ, autistic spectrum, developmental delay, intellectual disability, epilepsy all increased
- fairly large regions (100's kb to 100's mb)

Del22q – most common

20-30% get scz

present in 0.33% all cases, 0% controls

29-43 genes in region, 1.5-3mb

- 2 CNVs affect single genes – neurexin 1 (NRXN1) and vasoactive intestinal peptide receptor (VIPR2) enabling functional studies

However, more variation seems to be accounted for by common causal variants with incomplete penetrance

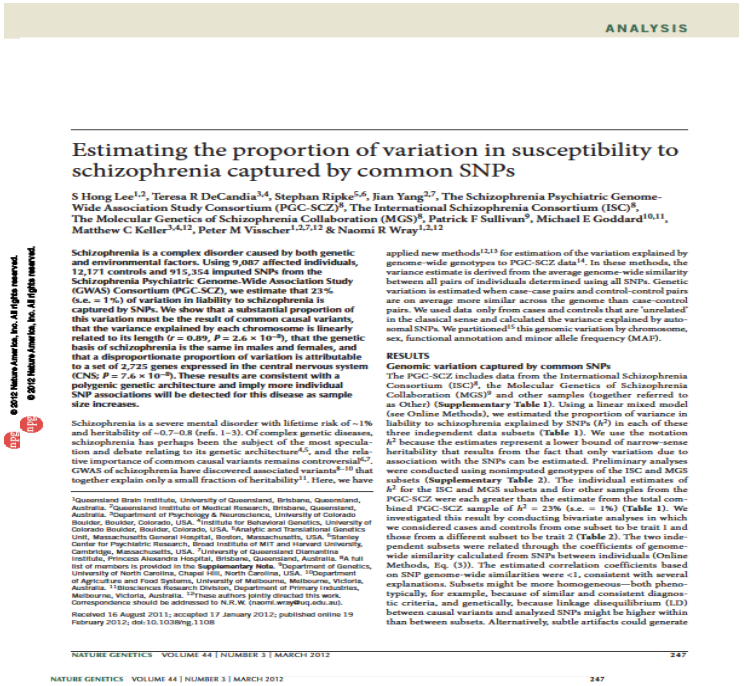
- Lee at al, with International consortia

March 2012

9000 cases, 12000 controls

nearly 1million SNPs

GCTA analysis



ANALYSIS

Estimating the proportion of variation in susceptibility to schizophrenia captured by common SNPs

S Hong Lee[1,2], Teresa R DeCandia[3,4], Stephan Ripke[5,6], Jian Yang[2,7], The Schizophrenia Psychiatric Genome-Wide Association Study Consortium (PGC-SCZ)[8], The International Schizophrenia Consortium (ISC)[8], The Molecular Genetics of Schizophrenia Collaboration (MGS)[8], Patrick F Sullivan[9], Michael E Goddard[10,11], Matthew C Keller[3,4,12], Peter M Visscher[1,2,7,12] & Naomi R Wray[1,2,12]

Schizophrenia is a complex disorder caused by both genetic and environmental factors. Using 9,087 affected individuals, 12,171 controls and 915,354 imputed SNPs from the Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium (PGC-SCZ), we estimate that 23% (s.e. = 1%) of variation in liability to schizophrenia is captured by SNPs. We show that a substantial proportion of this variation must be the result of common causal variants, that the variance explained by each chromosome is linearly related to its length ($r = 0.89$, $P = 2.6 \times 10^{-6}$), that the genetic basis of schizophrenia is the same in males and females, and that a disproportionate proportion of variation is attributable to a set of 2,725 genes expressed in the central nervous system (CNS; $P = 7.6 \times 10^{-6}$). These results are consistent with a polygenic genetic architecture and imply more individual SNP associations will be detected for this disease as sample size increases.

Schizophrenia is a severe mental disorder with lifetime risk of ~1% and heritability of ~0.7–0.8 (refs. 1–3). Of complex genetic diseases, schizophrenia has perhaps been the subject of the most speculation and debate relating to its genetic architecture[4,5], and the relative importance of common causal variants remains controversial[6,7]. GWAS of schizophrenia have discovered associated variants[8–10] that together explain only a small fraction of heritability[11]. Here, we have applied new methods[12,13] for estimation of the variation explained by genome-wide genotypes to PGC-SCZ data[14]. In these methods, the variance estimate is derived from the average genome-wide similarity between all pairs of individuals determined using all SNPs. Genetic variation is estimated when case–case pairs and control–control pairs are on average more similar across the genome than case–control pairs. We used data only from cases and controls that are 'unrelated' in the classical sense and calculated the variance explained by autosomal SNPs. We partitioned[15] this genomic variation by chromosome, sex, functional annotation and minor allele frequency (MAF).

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RESULTS

Genomic variation captured by common SNPs

The PGC-SCZ includes data from the International Schizophrenia Consortium (ISC)[8], the Molecular Genetics of Schizophrenia Collaboration (MGS)[8] and other samples (together referred to as Other) (**Supplementary Table 1**). Using a linear mixed model (see Online Methods), we estimated the proportion of variance in liability to schizophrenia explained by SNPs (h^2) in each of these three independent data subsets (**Table 1**). We use the notation h^2 because the estimates represent a lower bound of narrow-sense heritability that results from the fact that only variation due to association with the SNPs can be estimated. Preliminary analyses were conducted using nonimputed genotypes of the ISC and MGS subsets (**Supplementary Table 2**). The individual estimates of h^2 for the ISC and MGS subsets and for other samples from the PGC-SCZ were each greater than the estimate from the total combined PGC-SCZ sample of $h^2 = 23\%$ (s.e. = 1%) (**Table 1**). We investigated this result by conducting bivariate analyses in which we considered cases and controls from one subset to be trait 1 and those from a different subset to be trait 2 (**Table 2**). The two independent subsets were related through the coefficients of genome-wide similarity calculated from SNPs between individuals (Online Methods, Eq. (3)). The estimated correlation coefficients based on SNP genome-wide similarities were <1, consistent with several explanations. Subsets might be more homogeneous—both phenotypically, for example, because of similar and consistent diagnostic criteria, and genetically, because linkage disequilibrium (LD) between causal variants and analyzed SNPs might be higher within than between subsets. Alternatively, subtle artifacts could generate

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- accounted for 23% (s.e.1%) of variation in liability to schizophrenia
- variance explained by each chromosome is linearly related to its length
- genetic basis is the same in males and females
- disproportionate amount of variance is attributable to set of 2725 genes expressed in CNS
- confirmed highly polygenic genetic architecture

Genome-wide association study identifies five new schizophrenia loci

The Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium[1]

We examined the role of common genetic variation in schizophrenia in a genome-wide association study of substantial size: a stage 1 discovery sample of 21,856 individuals of European ancestry and a stage 2 replication sample of 29,839 independent subjects. The combined stage 1 and 2 analysis yielded genome-wide significant associations with schizophrenia for seven loci, five of which are new (1p21.3, 2q32.3, 8p23.2, 8q21.3 and 10q24.32-q24.33) and two of which have been previously implicated (6p21.32-p22.1 and 18q21.2). The strongest new finding ($P = 1.6 \times 10^{-11}$) was with rs1625579 within an intron of a putative primary transcript for *MIR137* (microRNA 137), a known regulator of neuronal development. Four other schizophrenia loci achieving genome-wide significance contain predicted targets of *MIR137*, suggesting *MIR137*-mediated dysregulation as a previously unknown etiologic mechanism in schizophrenia. In a joint analysis with a bipolar disorder sample (16,374 affected individuals and 14,044 controls), three loci reached genome-wide significance: *CACNA1C* (rs4765905, $P = 7.0 \times 10^{-9}$), *ANK3* (rs10994359, $P = 2.5 \times 10^{-8}$) and the *ITIH3-ITIH4* region (rs2239547, $P = 7.8 \times 10^{-9}$).

In stage 1, we conducted a mega-analysis combining genome-wide association study (GWAS) data from 17 separate studies (with a total of 9,394 cases and 12,462 controls; Table 1 and Supplementary Tables 1,2). We imputed allelic dosages for 1,252,901 autosomal SNPs (Table 1, Supplementary Table 3 and Supplementary Note) using HapMap3 as the reference panel[1]. We tested for association using logistic regression of imputed dosages with sample identifiers and three principal components as covariates to minimize inflation in significance testing caused by population stratification. The quantile-quantile plot (Supplementary Fig. 1) deviated from the null distribution with a population stratification inflation factor of $\lambda = 1.23$. However, λ_{1000}, a metric that standardizes the degree of inflation by sample size, was only 1.02, similar to that observed in other GWAS meta-analyses[2,3]. This deviation persisted despite comprehensive quality control and inclusion of up to 20 principal components (Supplementary Fig. 1). Thus, we interpret this deviation as indicative of a large number of weakly associated SNPs consistent with polygenic inheritance[4]. We also examined 298 ancestry-informative markers (AIMs) that reflect European-ancestry population substructure[5]. Unadjusted analyses showed greater inflation in the test statistics than we saw for all markers (AIMs $\lambda = 2.26$ compared to all markers $\lambda = 1.56$). After inclusion of principal components, the distributions of the test statistics did not differ between AIMs ($\lambda = 1.18$) and all markers ($\lambda = 1.23$), a result inconsistent with population stratification explaining the residual deviation seen in Supplementary Figure 1. Moreover, the results of a meta-analysis using summary results generated using study specific principal components (Supplementary Note) were highly correlated with those from the mega-analysis (Pearson correlation = 0.94, with a similar $\lambda = 1.20$; Supplementary Fig. 2). Of the ten SNPs in Table 2, four increased and six decreased in significance, suggesting that the most extreme values did not result from systematic inflation artifacts. Therefore, our primary analysis used unadjusted *P* values (nevertheless, see Table 2 for stage 1 *P* values adjusted for λ (ref. 6).

In stage 1 (Table 2, Supplementary Table 4 and Supplementary Figs. 3 and 4), 136 associations reached genome-wide significance ($P < 5 \times 10^{-8}$)[7]. The majority of these associations ($N = 129$) mapped to 5.5 Mb in the extended major histocompatibility complex (MHC, 6p21.32-p22.1), a region of high linkage disequilibrium (LD) previously implicated in schizophrenia in a subset of the samples used here[4,8,9]. The other stage 1 regions included new regions (10q24.33 and 8q21.3) and previously reported regions (18q21.2 at *TCF4* (encoding transcription factor 4) and 11q24.2 (ref. 8)). The signal at 11q24.2 is ~0.85 Mb from *NRGN* (encoding neurogranin) and is uncorrelated with the previously associated variant near this gene[8].

In Table 2 and Supplementary Table 4, we denote regions of association by the most significant marker. Associated SNPs with $r^2 \geq 0.2$ in HapMap3 (CEU+TSI populations) were not considered independent. However, we noticed instances where multiple SNPs within 250 kb of each other yielded evidence for association ($P < 10^{-5}$) despite weak LD ($r^2 < 0.2$) between them. For regions with $P < 10^{-6}$, we performed a conditional analysis using as covariates the dosages of the strongest associated SNP, principal components 1–4 and 6 and study indicator. We observed multiple statistically independent signals at the MHC. Although a number of SNPs within the MHC were potentially independent per HapMap r^2 values, only rs9272105 withstood formal conditional analysis, showing $P = 1.8 \times 10^{-6}$ conditional on association to the best SNP, rs2021722 (stage 1 $P = 4.3 \times 10^{-11}$, inter-SNP distance = 2.4 Mb, $r^2 = 0.01$ in HapMap). Excluding the MHC region, we identified six regions with at least one SNP associated at $P < 10^{-5}$ and a second SNP with a conditionally independent $P < 10^{-3}$

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Discovery sample=22,000
Replication sample = 30,000 (independent)
October 2011

7 loci, 5 new

Strongest new finding
miRNA-137
known regulator of neuronal development, highly expressed in synapses of cortex, hippocampus

4 other loci were in regions of binding sites for this miRNA

Joint analysis w. 30,000 bipolar subjects & controls showed 3 loci in common

Validation of schizophrenia associated genes CSMD1, C10orf26, CACNA1C and TCF4 as miR-137 targets

Molecular Psychiatry (2013) 18, 11--12;

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Molecular Psychiatry website (http://www.nature.com/mp)

Validation of schizophrenia-associated genes *CSMD1*, *C10orf26*, *CACNA1C* and *TCF4* as miR-137 targets

Molecular Psychiatry (2013) **18**, 11–12; doi:10.1038/mp.2011.170; published online 20 December 2011

A recently completed genome-wide association study (GWAS) implicated single-nucleotide polymorphisms in the *MIR137* gene as being highly associated with schizophrenia.[1] *MIR137* encodes for the microRNA miR-137, which has been implicated in the regulation of adult neurogenesis[2] and neuron maturation.[3] Strikingly, four predicted targets of miR-137 also achieved genome-wide significance. These findings suggest that the dysregulation or dysfunction of miR-137 may be a novel pathological pathway underlying the etiology of schizophrenia. In this work, we use a luciferase-based reporter assay to demonstrate the site-specific regulation of *CSMD1*, *C10orf26*, *CACNA1C* and *TCF4* by miR-137.

Schizophrenia is a spectrum disorder that has a lifetime prevalence of ~1%. Disease onset usually occurs during adolescence, and suicide is the leading cause of premature death. Although monozygotic twin studies have clearly shown a genetic basis for this disease, the underlying genetics of schizophrenia have been difficult to delineate. A linkage study of a Scottish family with a high incidence of psychiatric disorders identified a rare, but highly penetrant, mutation in disrupted in schizophrenia-1 (*DISC1*);[4] however, single-gene mutations have not been found in the vast majority of schizophrenia patients. It is believed that the onset of schizophrenia is due to the accumulation of several gene mutations, each of which has modest phenotypic effects, which are compounded with environmental factors. This complexity has made the identification of contributing genes difficult. Improvements in genotyping technology have allowed for GWAS in large patient populations. However, the results of schizophrenia GWASs have yet to be validated biologically.

In a recent study by the Schizophrenia Psychiatric GWAS consortium, *MIR137*, along with four of its putative targets (*CSMD1*, *C10orf26*, *CACNA1C* and *TCF4*) were reported to have genome-wide significant associations with schizophrenia.[1] In addition, genes associated with schizophrenia were enriched for predicted miR-137 targets. These findings imply that miR-137 dysregulation or dysfunction may be a pathway that contributes to schizophrenia disease progression. Until this report, schizophrenia GWAS findings have not been linked to the neurobiology of the disease. To investigate the biological relevance of schizophrenia GWAS findings, we used reporter constructs to directly confirm miR-137-mediated knockdown of predicted miR-137 target sequences in the 3′-untranslated regions of four putative schizophrenia risk genes.

The *CSMD1*, *C10orf26*, *CACNA1C* and *TCF4* predicted miR-137 target gene 3′-untranslated regions have either 7mer or 8mer canonical sites and, in some cases, are elaborated with a 3′-supplementary site (Figure 1a), as defined previously.[5] These five sites (*TCF4* has two predicted miR-137 sites) and their flanking sequences were cloned into the 3′-untranslated region of Renilla luciferase in the psiCHECK-2 vector (Figure 1b) and co-transfected with either miR-CNTL or miR-137 overexpression constructs at a 1:2 ratio into HEK-293T cells using Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA). HEK-293T cells have a low endogenous level of miR-137 expression (data not shown). The psiCHECK-2 vector also includes Firefly luciferase driven by a separate promoter that allows for normalization of signal to transfection efficiencies. When the ratio of Renilla to Firefly luciferase activity was compared between cells transfected with miR-CNTL and those with miR-137, all predicted targeted showed decreased Renilla luciferase activities by 25–50% compared with controls (Figure 1c). When the miR-137 7mer site 5′-GCAAUAA-3′ was deleted from each target construct and co-transfected with miR-137, the Renilla/Firefly luciferase ratio did not differ significantly from controls ($P > 0.05$ two-way analysis of variance). These results show that miR-137 interacts with the 3′-untranslated region sequences from the four predicted targets in a site-specific manner.

MiR-137 has been shown to have a role in epigenetic regulation of adult neural stem cell proliferation[2] and neuronal maturation.[3] This is analogous to the phenotypes following knockdown of the schizophrenia-related gene *DISC1*.[6] In addition, two predicted miR-137 targets have been previously associated with psychiatric illness. *CACNA1C* encodes for the α subunit of the voltage-dependent L-type calcium channel $Ca_V1.2$, and has been shown to be associated with bipolar disease.[7] *TCF4* encodes a transcription factor involved in the development of a subset of neural progenitors[8] and TCF4-overexpressing transgenic mice show schizophrenia-associated behavior.[9] These studies, and the recent

Single genes from replicated studies, effects currently being associated with phenotypic effects

With samples of 34,000 22 loci now identified 50,000 sample being analysed

miRNA 137

CACNA1C calcium channel SCZ and bipolar (BIP) autism

calcium channel modifiers used as treatment for BIP

neurogranin (NRGN) calcium sensor SCZ and BIP

neurocan (NCAN) extracellular matrix protein SCZ and BIP

neurexins - presynaptic membrane proteins found in ALL neurons

cause decrease in prepulse inhibition, global excitation in knock-out mice

extended MHC HLA region chr 6

Chlamydial infection and HLA-A genotype associated with SCZ?

- epigenetic phenomena

differences in methylation patterns may account for some MZ discordance (female discordance is greater than male)

genetic heterogeneity – similar phenotype produced by different risk alleles in different people

Increased inflammatory markers identified in the dorsolateral prefrontal cortex of individuals with schizophrenia

SG Fillman[1,2,3], N Cloonan[4], VS Catts[1,2,3], LC Miller[5], J Wong[6], T McCrossin[7], M Cairns[1,8] and CS Weickert

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ORIGINAL ARTICLE

Increased inflammatory markers identified in the dorsolateral prefrontal cortex of individuals with schizophrenia

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Upregulation of the immune response may be involved in the pathogenesis of schizophrenia with changes occurring in both peripheral blood and brain tissue. To date, microarray technology has provided a limited view of specific inflammatory transcripts in brain perhaps due to sensitivity issues. Here we used SOLiD Next Generation Sequencing to quantify neuroimmune mRNA expression levels in the dorsolateral prefrontal cortex of 20 individuals with schizophrenia and their matched controls. We detected 798 differentially regulated transcripts present in people with schizophrenia compared with controls. Ingenuity pathway analysis identified the inflammatory response as a key change. Using quantitative real-time PCR we confirmed the changes in candidate cytokines and immune modulators, including interleukin (IL)-6, IL-8, IL-1β and SERPINA3. The density of major histocompatibility complex-II-positive cells morphologically resembling microglia was significantly increased in schizophrenia and correlated with IL-1β expression. A group of individuals, most of whom had schizophrenia, were found to have increased inflammatory mRNA expression. In summary, we have demonstrated changes in an inflammatory response pathway that are present in ~40% of people diagnosed with schizophrenia. This suggests that therapies aimed at immune system attenuation in schizophrenia may be of direct benefit in the brain.

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Keywords: immune; inflammatory; microglia; next generation sequencing; schizophrenia

INTRODUCTION

Schizophrenia is a severe neuropsychiatric disorder affecting around 1% of the world's population. Current treatments are ineffective at addressing the full spectrum of symptoms. Understanding schizophrenia's causes will allow us to better tailor the treatments to specific biological subgroups, which may be present under the broad diagnostic group of schizophrenia. Previous studies have used microarrays to examine the brain transcriptome of individuals with schizophrenia to establish patterns of gene expression changes implicating GABAergic, synaptic and myelin pathways, as well as inflammatory/immune response.[1–6] However, microarray studies have been limited by target specificity, restricted linear range and background interference.[7,8] Next-generation sequencing (NGS), specifically RNA-Seq, overcomes these problems through the use of massively parallel nucleotide sequencing of small sections of the transcriptome and digital reassembly of the reads, resulting in no upper limit to quantification and a very sensitive detection threshold.[7]

The immune system's role in schizophrenia is somewhat controversial but evidence from genomic, blood, postmortem and *in vivo* imaging studies are leading toward a greater consensus that immune activation is involved.[9–12] A significant positive genetic association between schizophrenia and the human leukocyte antigen (HLA) locus responsible for major histocompatibility complex (MHC) expression and the genetic region containing cytokines interleukin (IL)-1α, IL-1β and IL1RA have been found.[13–15] Serum cytokines are also significantly increased in schizophrenia (IL-6, IL-8).[10,16–21] Elevations in expression of other immune-related genes, but not cytokines, have been found in the dorsolateral prefrontal cortex (DLPFC) of individuals with schizophrenia.[1,5] In brain, cytokines are synthesized and secreted by the resident immune cells and microglia, among others. Microglia have diverse functions including serving as antigen-presenting cells through the MHC-II receptor.[22–24] Brain microglia have been measured using *in vivo* positron emission tomography and *in vitro* binding with significant increases in (^{11}C)PK-11195 binding observed in people with schizophrenia compared with controls in two out of three studies.[25–27] This evidence would indicate that there is a subset of living individuals with schizophrenia who may have increased immune responses in their brain. Thus, we hypothesized that we would detect increased microglia density and increased mRNA levels of pro-inflammatory cytokines in the brains of people with schizophrenia.

The current study is among the first to use NGS to examine the transcriptome of DLPFC from 20 individuals with schizophrenia and 20 matched controls, providing the most sensitive examination of gene expression changes in schizophrenia available to date. In addition, the RNA-Seq results were confirmed by quantitative PCR (qPCR) in an expanded cohort ($n = 74$) in which microglial density was also measured through immunohistochemistry, cell counting, and western blotting.

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Evidence for overlap in risk alleles between SCZ and BIP

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IMMEDIATE COMMUNICATION

Gene-wide analyses of genome-wide association data sets: evidence for multiple common risk alleles for schizophrenia and bipolar disorder and for overlap in genetic risk

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Genome-wide association (GWAS) analyses have identified susceptibility loci for many diseases, but most risk for any complex disorder remains unattributed. There is therefore scope for complementary approaches to these data sets. Gene-wide approaches potentially offer additional insights. They might identify association to genes through multiple signals. Also, by providing support for genes rather than single nucleotide polymorphisms (SNPs), they offer an additional opportunity to compare the results across data sets. We have undertaken gene-wide analysis of two GWAS data sets: schizophrenia and bipolar disorder. We performed two forms of analysis, one based on the smallest *P*-value per gene, the other on a truncated product of *P* method. For each data set and at a range of statistical thresholds, we observed significantly more SNPs within genes (P_{min} for excess < 0.001) showing evidence for association than expected whereas this was not true for extragenic SNPs (P_{min} for excess > 0.1). At a range of thresholds of significance, we also observed substantially more associated genes than expected (P_{min} for excess in schizophrenia = 1.8×10^{-4}, in bipolar = 2.4×10^{-6}). Moreover, an excess of genes showed evidence for association across disorders. Among those genes surpassing thresholds highly enriched for true association, we observed evidence for association to genes reported in other GWAS data sets (*CACNA1C*) or to closely related family members of those genes including *CSF2RB*, *CACNA1B* and *DGKI*. Our analyses show that association signals are enriched in and around genes, large numbers of genes contribute to both disorders and gene-wide analyses offer useful complementary approaches to more standard methods.
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Keywords: genetics; association; bipolar; schizophrenia; psychosis

Introduction

Until recently, there have been few undisputed genetic associations to non-Mendelian forms of common human diseases, but for many diseases, the advent of genome-wide association (GWAS) technology has recently transformed this position.[1] The attainment of highly significant associations though GWAS reflects in some cases, the availability of large sample sizes,[2] for others, for example the HLA locus in rheumatoid arthritis and T1D, the existence of at least some common alleles with a greater than average effect size.[3] These conditions may not readily be satisfied for most complex disorders, for example psychotic disorders, where the extremely large sample sizes used for some disorders[2] are difficult to obtain because diagnosis is labourious and expensive. Moreover, the necessary use of phenotypes entirely defined by symptoms will very likely increase aetiological heterogeneity, and thus the observed correlations between genotypes and phenotypes. Therefore far from having a few common risk genes with higher than expected effect sizes, the observed effect sizes in psychosis might be even smaller than those typical for other complex disorders. Moreover, even for those disorders where successes have been legion, the majority of genetic risk remains unattributed.[2,4] There is therefore a pressing need for alternative methods for extracting information from GWAS data sets.

GWAS studies to date have focused on single locus tests, which are the simplest to generate and to

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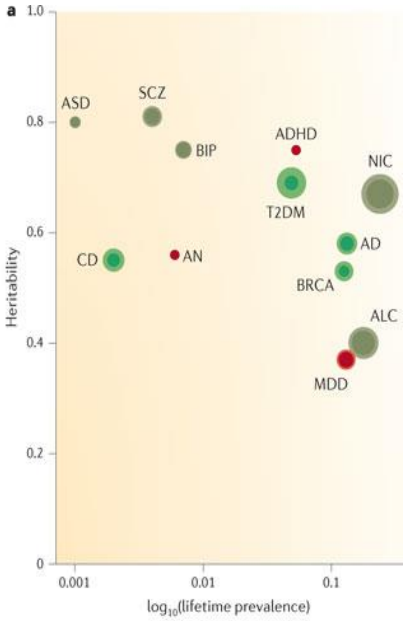
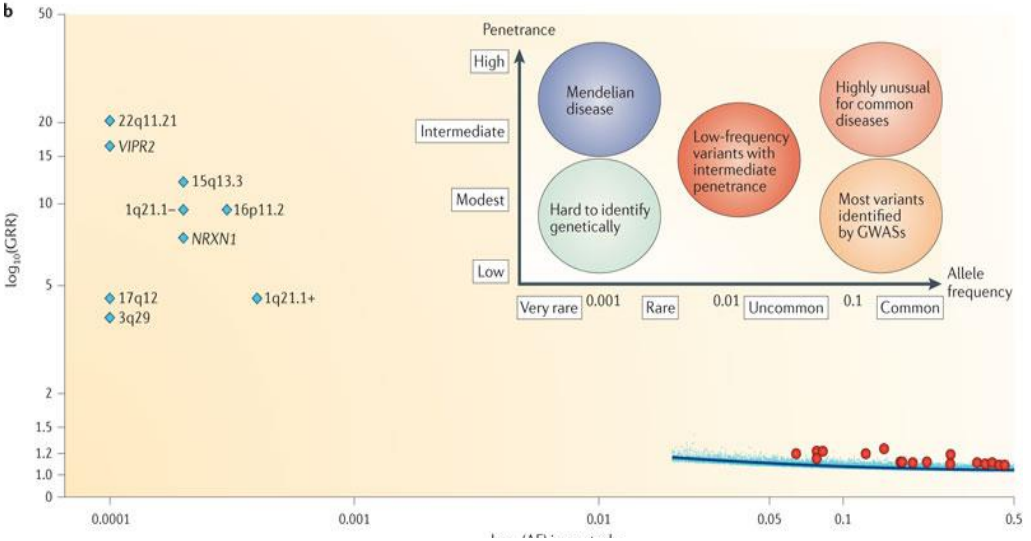
a | Plot of heritability by log10(lifetime prevalence) for the nine psychiatric disorders considered in this Review plus three complex diseases for which genetic dissection has been particularly successful . Each disorder is plotted as heritability by lifetime prevalence. Colour indicates qualitative success in identifying aetiological genetic variation (with bright green meaning notably successful, dark green meaning some successes and red meaning minimal or no clear success to date). The bubble sizes are proportional to the numbers of cases studied in GWASs

b | Allelic spectrum of schizophrenia (SCZ). There are no known Mendelian variants for SCZ (AF<<0.0001, GRR>>50). There are no known common variants (AF>0.1) with GRR>1.5, and these can be excluded with >99% statistical power. Nine structural variants associated with SCZ are shown as light blue diamonds (1q21.1– is the deletion and 1q21.1+ is the duplication). These structural variants do not have a corresponding region in the inset. Seventeen common variants have been associated with SCZ (red circles). SNPs contributing to the Psychiatric Genomics Consortium SCZ risk profile score59 (21,171 autosomal SNPs with P T<0.1; BOX 3, panel b) are shown in light blue dots with a lowess smoother in dark blue. AD, Alzheimer's disease; ADHD, attention-deficit hyperactivity disorder; ALC, alcohol dependence; AN, anorexia nervosa; ASD, autism spectrum disorder; BIP, bipolar disorder; BRCA, breast cancer; CD, Crohn's disease; MDD, major depressive disorder; NIC, nicotine usage (maximum cigarettes per day); SCZ, schizophrenia; T2DM, type 2 diabetes mellitus. The inset in panel b is adapted, with permission, from Ref. 10 © (2008) Macmillan Publishers Ltd. All rights reserved.



GRR genotypic relative risk
AF allele frequency in controls



Progress in finding useful biomarkers

Open

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ORIGINAL ARTICLE

Potential metabolite markers of schizophrenia

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Schizophrenia is a severe mental disorder that affects 0.5–1% of the population worldwide. Current diagnostic methods are based on psychiatric interviews, which are subjective in nature. The lack of disease biomarkers to support objective laboratory tests has been a long-standing bottleneck in the clinical diagnosis and evaluation of schizophrenia. Here we report a global metabolic profiling study involving 112 schizophrenic patients and 110 healthy subjects, who were divided into a training set and a test set, designed to identify metabolite markers. A panel of serum markers consisting of glycerate, eicosenoic acid, β-hydroxybutyrate, pyruvate and cystine was identified as an effective diagnostic tool, achieving an area under the receiver operating characteristic curve (AUC) of 0.945 in the training samples (62 patients and 62 controls) and 0.895 in the test samples (50 patients and 48 controls). Furthermore, a composite panel by the addition of urine β-hydroxybutyrate to the serum panel achieved a more satisfactory accuracy, which reached an AUC of 1 in both the training set and the test set. Multiple fatty acids and ketone bodies were found significantly ($P < 0.01$) elevated in both the serum and urine of patients, suggesting an upregulated fatty acid catabolism, presumably resulting from an insufficiency of glucose supply in the brains of schizophrenia patients.
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Keywords: schizophrenia; biomarker; metaobonomics; GC-TOFMS; NMR

Introduction

Schizophrenia is a severe mental disorder affecting approximately 0.5–1% of the population worldwide.[1] As one of the most expensive medical illness, schizophrenia represents a serious burden on the health-care system.[2] Clinically, it has heterogeneous presentations, with positive and negative symptoms at different levels of prominence across time and across individuals.[3] The current diagnosis of schizophrenia remains subjective due to its complex spectrum of symptoms, and the mechanism underlying the disease process has yet to be elucidated.

Recent clinical studies suggest that early intervention mitigates progression and improves therapeutic outcomes in the disease.[4–6] Establishment of biomarkers will enable early disease prevention, and thus improve prognosis. A niacin test proposed to measure reduced membrane arachidonic acid levels was suggested for the diagnosis of schizophrenia in 1980,[7] but has not found its way into clinical use so far owing to its low sensitivity and specificity.[8–10] Imaging modalities including functional magnetic resonance imaging, positron emission tomography and single-photon emission computerized tomography (SPECT), although frequently used in the pathological study of schizophrenia,[11] have not been able to offer a diagnostic solution with a high enough sensitivity and specificity. Recently, genetic variants at the major histocompatibility complex locus have been found significantly associated with this disease from several major genome-wide association studies,[12–14] suggesting an immune component in its

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Marked reduction of soluble superoxide dismutase-1 (SOD1) in cerebrospinal fluid of patients with recent-onset schizophrenia

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Recent schizophrenia research supports a model, wherein aberrant brain changes in late-adolescence contribute to the onset and early progression of disease.[1] To further examine this model, longitudinal studies of genetic high-risk subjects, including those in prodromal stage, have recently been conducted.[2] Parallel studies evaluating patients with recent-onset schizophrenia are growing in number.[3] Nonetheless, almost all these studies are limited to clinical and neuropsychological characterization, and to brain imaging. Therefore, the molecular mechanisms underlying these dynamic changes remain elusive.

In order to address this fundamental question with better molecular understanding, we have examined the cerebrospinal fluid (CSF) from patients with recent-onset schizophrenia (within the first five years of disease) and have compared these samples to those from age-matched healthy controls and patients with chronic schizophrenia (five or more years of schizophrenia) (Supplementary Table 1). Building on the hypothesis that oxidative stress and associated neuroinflammatory response may have a role in this dynamic process,[4] we measured the levels of 14 selected molecules (Supplementary Table 2).

Here, we report the novel finding of a dramatically reduced level of soluble superoxide dismutase-1 (SOD1) in CSF from patients with recent-onset schizophrenia in contrast to samples from age-matched healthy controls (Table 1, Supplementary Figure 1). Furthermore, the level of CSF-soluble SOD1 from recent-onset patients is lower than that from patients with chronic schizophrenia. To our knowledge, this is the first report of decreased CSF SOD1 in recent-onset schizophrenia. We also highlight that although the sample size of patients with 1 year or less disease is small, the absolute concentrations of soluble SOD1 are most robustly decreased in this cohort. We speculate that the decrease in soluble SOD1 between patients with 1 year or less disease and age-matched healthy controls is limited in significance by the small sample size.

Although our reported observations require replication in a larger sample, this study implies two innovative conceptual contributions. First, the reduction of soluble SOD1 may directly underlie oxidative stress at the onset of schizophrenia through decreased availability of this important antioxidant enzyme. We further note that this decrease in CSF-soluble SOD1 concentration could be a secondary effect of another pro-oxidative process. Nevertheless, this ultimate decrease in soluble SOD1 is likely to facilitate overall oxidative stress. Thus, we provide further evidence of the 'oxidative stress hypothesis' in schizophrenia. Second, we note the possibility that a decrease in CSF-soluble SOD1 may reflect an increase in 'insoluble' SOD1. This is analogous to decreased Aβ1-42 in CSF from patients with Alzheimer's disease reflecting insoluble Aβ1-42 and senile plaques.[5] Likewise, SOD1 is amyloidogenic and can be associated with brain disorders, such as amyotrophic lateral sclerosis.[6] We wish to recall that aggregate formation in Huntington's disease and other brain disorders has been discovered only after specific probing of target molecules, such as *Huntingtin* detection using a specific antibody.[7] Therefore, it is crucial to now explore insoluble SOD1 in autopsied brains or biopsied cells (for example, induced neurons from fibroblasts, and olfactory neurons) from patients with recent-onset schizophrenia, and such future studies may utilize antibodies against insoluble forms of SOD1.[8] A role of misfolded protein in schizophrenia has also been suggested by studies stemming from genetic susceptibility factors. Korth and associates[9] reported the recruitment of Dysbindin protein to cell-invasive DISC1 aggresomes, suggesting the important convergence of two promising genetic risk factors and the significance of protein insolubility in cases of schizophrenia.

The levels of CSF-soluble SOD1 are not significantly different between chronic cases and matched healthy controls (data not shown). The possible contrast in SOD1 between recent-onset schizophrenia and chronic cases may be addressed in follow-up studies with larger sample size. It is possible that transient downregulation around the onset of schizophrenia might have an important pathophysiological role. Of note, some studies suggest that neuroleptic medication might increase plasma or serum SOD levels,[10] although levels between peripheral blood and CSF are not necessarily correlated. In this report, with one exception, all patients were on medication at the time of CSF acquisition.

In summary, we report diminished CSF-soluble SOD1 in cases of recent-onset schizophrenia and discuss this observation as supporting the previously proposed role of 'oxidative stress' in the pathophysiology and onset of this disease. Increased oxidative stress can lead to synaptic deterioration and interneuron deficits relevant to the pathophysiology of schizophrenia. Furthermore, this observation may also be an entry point for other working hypotheses, such as those of SOD1 protein misfolding and aberrant control of proteolysis, which prompt further investigation.

Table 1. Comparison of CSF-soluble SOD1 concentration between patients with recent-onset schizophrenia (less than five years disease) grouped by disease duration and age-matched healthy controls

Disease duration (years)	*N, matched pairs*	*SZ mean (ng ml^{-1})*	*HC mean (ng ml^{-1})*	*T*	*P*	*P**
⩽1	15	65.19 ± 27.55	110.93 ± 64.55	−2.55	0.023	0.12
⩽2[a]	20	74.16 ± 41.77	115.35 ± 59.89	−2.91	0.009	0.06
⩽3	25	74.88 ± 37.56	116.00 ± 61.33	−3.28	0.003	0.02
⩽4	32	74.94 ± 38.44	107.55 ± 57.32	−3.00	0.005	0.04

Abbreviations: CSF, cerebrospinal fluid; HC, healthy control; SOD1, superoxide dismutase-1; SZ, schizophrenia.
*P** is the empirical *p* value corrected for the multiple testing of 14 selected markers derived by permutation (see Supplementary Methods for description of the permutation procedure and Supplementary Table 2 for results of analysis with the other markers).
[a]Individuals with less disease duration were included in subsequent groups of cases with increased years or less disease. Age matching of controls was completed independently for each of these four groups of increasing disease duration.

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ORIGINAL ARTICLE

Relapse prevention in schizophrenia: a systematic review and meta-analysis of second-generation antipsychotics versus first-generation antipsychotics

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Few controlled trials compared second-generation antipsychotics (SGAs) with first-generation antipsychotics (FGAs) regarding relapse prevention in schizophrenia. We conducted a systematic review/meta-analysis of randomized trials, lasting ⩾6 months comparing SGAs with FGAs in schizophrenia. Primary outcome was study-defined relapse; secondary outcomes included relapse at 3, 6 and 12 months; treatment failure; hospitalization; and dropout owing to any cause, non-adherence and intolerability. Pooled relative risk (RR) (±95% confidence intervals (CIs)) was calculated using random-effects model, with numbers-needed-to-treat (NNT) calculations where appropriate. Across 23 studies (n=4504, mean duration=61.9±22.4 weeks), none of the individual SGAs outperformed FGAs (mainly haloperidol) regarding study-defined relapse, except for isolated, single trial-based superiority, and except for risperidone's superiority at 3 and 6 months when requiring ⩾3 trials. Grouped together, however, SGAs prevented relapse more than FGAs (29.0 versus 37.5%, RR=0.80, CI: 0.70–0.91, P=0.0007, I^2=37%; NNT=17, CI: 10–50, P=0.003). SGAs were also superior regarding relapse at 3, 6 and 12 months (P=0.04, P<0.0001, P=0.0001), treatment failure (P=0.003) and hospitalization (P=0.004). SGAs showed trend-level superiority for dropout owing to intolerability (P=0.05). Superiority of SGAs regarding relapse was modest (NNT=17), but confirmed in double-blind trials, first- and multi-episode patients, using preferentially or exclusively raw or estimated relapse rates, and for different haloperidol equivalent comparator doses. There was no significant heterogeneity or publication bias. The relevance of the somewhat greater efficacy of SGAs over FGAs on several key outcomes depends on whether SGAs form a meaningful group and whether mid- or low-potency FGAs differ from haloperidol. Regardless, treatment selection needs to be individualized considering patient- and medication-related factors.

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Keywords: antipsychotics; long-term treatment; maintenance; meta-analysis; relapse prevention; schizophrenia

Introduction

As psychopathology and social functioning can worsen with repeated relapses in schizophrenia patients,[1] relapse prevention is a critical issue in managing this illness. Since clozapine, the first second-generation antipsychotic (SGA) introduced in 1971 (marketed in the United States of America in 1990), and risperidone, introduced in 1994, a total of eight additional SGAs are now available in the United States of America, which are widely used.[2] SGAs are better tolerated than first-generation antipsychotics (FGAs) regarding acute extra-pyramidal side effects (EPS)[3] and tardive dyskinesia.[4] However, there is growing concern about metabolic side effects, such as body weight gain, insulin resistance and dyslipidemia.[5,6] Combined with the lack of significant superiority in efficacy and/or effectiveness observed in large, pragmatic trials,[7–10] the advantages of non-clozapine SGAs over FGAs have been challenged. Less attention has been focused on relapse prevention. A meta-analysis comparing SGAs to FGAs was published in 2003,[11] but since then, there have been 12 additional relevant trials.

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Part of the data was presented in poster format at the 51st Annual Meeting of the New Clinical Drug Evaluation Unit (NCDEU), Boca Raton, FL, USA, 15 June 2011.
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EXPERT REVIEW

The emerging spectrum of allelic variation in schizophrenia: current evidence and strategies for the identification and functional characterization of common and rare variants

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After decades of halting progress, recent large genome-wide association studies (GWAS) are finally shining light on the genetic architecture of schizophrenia. The picture emerging is one of sobering complexity, involving large numbers of risk alleles across the entire allelic spectrum. The aims of this article are to summarize the key genetic findings to date and to compare and contrast methods for identifying additional risk alleles, including GWAS, targeted genotyping and sequencing. A further aim is to consider the challenges and opportunities involved in determining the functional basis of genetic associations, for instance using functional genomics, cellular models, animal models and imaging genetics. We conclude that diverse approaches will be required to identify and functionally characterize the full spectrum of risk variants for schizophrenia. These efforts should adhere to the stringent standards of statistical association developed for GWAS and are likely to entail very large sample sizes. Nonetheless, now more than any previous time, there are reasons for optimism and the ultimate goal of personalized interventions and therapeutics, although still distant, no longer seems unattainable.

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Keywords: CNV; functional genomics; GWAS; schizophrenia; sequencing; SNP

THE NATURE OF THE PROBLEM

Schizophrenia is a chronic psychiatric disorder characterized by delusional beliefs, auditory hallucinations, disorganized thought and behaviour, negative symptoms, and cognitive deficits producing profound impairment of emotional and social behaviour. Onset of psychosis is typically in late adolescence or early adulthood, although subtle, nonspecific signs such as delayed milestones[1] and reduced intelligence quotient[2] predate psychosis onset. These data are consistent with a reformulation of illness comprising pre-symptomatic risk, prodrome, acute psychosis and chronic illness.[3] The schizophrenia phenotype is defined according to reliable international criteria (DSM-IV; ICD-10), but is nonetheless heterogeneous and is generally thought to comprise an amalgam of related disorders, a plurality that was proclaimed in the title of Bleuler's classic 1911 text, 'Dementia praecox or the group of schizophrenias'.[4] Over the subsequent 100 years, many attempts have been made to carve schizophrenia 'at its joints' in order to develop homogeneous sub-types for more intensive aetiological study. The deficit syndrome,[5] and antipsychotic treatment resistance[6] serve as examples. In parallel with this drive to refine, is the more recent trend, based on accumulating evidence, to question the 'Kraepelinian divide' between schizophrenia and bipolar disorder.[7]

Lifetime prevalence for established illness is ~0.72%[8] and the suicide rate is ~7%, the majority occurring in the first 3 years after onset.[9] Only a minority (<14%) experience sustained recovery within the first 5 years of illness[10] and another 16% later in the illness.[11] Current treatments have limited efficacy (80% relapse rates)[10] and financial costs are high (for example, €94 billion for psychotic disorders in Europe, 2010),[12] with attendant medical complications (obesity, nicotine dependence, metabolic syndrome and premature mortality), low employment[13] and substantial homelessness.[14] The disorder ranks ninth in the global burden of illness, and ranks fifth (males) and sixth (females) in the leading global causes of years lost because of disability.[15]

Despite the magnitude of its disease burden, the aetiology of schizophrenia remains poorly understood. The prevailing hypothesis is that schizophrenia is a neurodevelopmental disorder,[16–18] but the underlying molecular and cellular mechanisms remain a mystery. Diverse aetiological clues, including family history, early life adversity, urban upbringing, migrant status, cannabis use and a variety of pre/perinatal factors,[19] have emerged from a large body of epidemiological studies.[20] By far the most compelling of these is family history, recognized for almost a century since Kraepelin observed 'dementia praecox not at all infrequently is familial, often appearing in brothers and sisters'.[21] Decades of family, twin and adoption studies have established high heritability (81%, confidence interval: 73–90%),[22,23] which has compelled the search for genetic variation contributing to disease.

THE PRE-GWAS ERA

Before the development of genome-wide association study (GWAS) methodology, genetic studies of schizophrenia relied on karyotyping, linkage studies and candidate gene association studies. Two of the best-known chromosomal rearrangements are large deletions on chromosome 22q11.2 and a balanced chromosomal translocation t(1:11) (q43;q21) that led to the discovery of the *DISC1* (disrupted-in-schizophrenia 1) gene. The chromosome 22q11.2 deletion syndrome (22q11.2DS) occurs in 1

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Looking for expression pattern differences

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ORIGINAL ARTICLE

Genome-wide expression profiling of schizophrenia using a large combined cohort

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Numerous studies have examined gene expression profiles in post-mortem human brain samples from individuals with schizophrenia compared with healthy controls, to gain insight into the molecular mechanisms of the disease. Although some findings have been replicated across studies, there is a general lack of consensus on which genes or pathways are affected. It has been unclear if these differences are due to the underlying cohorts or methodological considerations. Here, we present the most comprehensive analysis to date of expression patterns in the prefrontal cortex of schizophrenic, compared with unaffected controls. Using data from seven independent studies, we assembled a data set of 153 affected and 153 control individuals. Remarkably, we identified expression differences in the brains of schizophrenics that are validated by up to seven laboratories using independent cohorts. Our combined analysis revealed a signature of 39 probes that are upregulated in schizophrenia and 86 that are downregulated. Some of these genes were previously identified in studies that were not included in our analysis, while others are novel to our analysis. In particular, we observe gene expression changes associated with various aspects of neuronal communication and alterations of processes affected as a consequence of changes in synaptic functioning. A gene network analysis predicted previously unidentified functional relationships among the signature genes. Our results provide evidence for a common underlying expression signature in this heterogeneous disorder.
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Keywords: schizophrenia; gene expression; microarray; post-mortem brain; prefrontal cortex

Introduction

Schizophrenia is a severe psychotic disorder that affects approximately 1% of the population worldwide.[1] Many groups have attempted to identify changes in gene expression in the brains of schizophrenics, often focusing on the prefrontal cortex.[2–4] Such studies have suggested several altered molecular processes including (but not limited to) synaptic machinery and mitochondrial-related transcripts,[5–8] immune function[8] and a reduction in oligodendrocyte and myelination-related genes.[10–12] The variety and scope of these processes, found in different subject cohorts, raises the question as to whether there are underlying commonalities in molecular signatures among schizophrenics. Such commonalities are presupposed by most genetic studies, which look for alleles overrepresented in large numbers of schizophrenic individuals.[13–15] It is important to establish if there are any common features of the disease at the molecular level.

The diversity of results in transcriptome studies can be attributed to many sources. Besides differences in the sampled cohorts and disease heterogeneity, discrepancies between transcriptome studies can be due to methodological differences in sample preparation, choice of platform and data analysis. There are issues that are especially pertinent to the analysis of post-mortem human brain tissue. One is the confounding effect of factors such as age, gender and medication. Such factors are often associated with relatively large gene expression changes,[16] while psychiatric illnesses such as schizophrenia are associated with small effect sizes. If these factors are not correctly controlled for, they can mask or masquerade as expression patterns associated with the disease. Standard practice involves minimizing the effects of such factors either in the experimental design by sample matching or treating these factors as covariates in regression models. It is also increasingly appreciated that technical artifacts such as 'batch effects' can result in substantial variability.[17–20] In addition, post-mortem brain tissue is a limited resource, leading to small sample sizes with low

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Mood disorders

- episodes of severe swings of mood

2 categories studied in behavior genetics:

Major depressive disorder (episodes of depression only)

Bipolar disorder (alternating episodes of depression and mania)

Major Depressive disorder (MDD)

WHO : #1 cause of disability in US, #2 worldwide

depressed mood

- onset over weeks/months, lasts several months, dissipates slowly
- loss of interest in usual activities
- sleep and appetite disturbances
- energy loss
- thoughts of death, suicide

US 16% risk of attempts : 4-5 times rate of other Axis I disorders

antidepressants = 2nd most widely sold drugs (1st=analgesics)

3rd cause of death 15-24 age group, 4th cause 25-44 age group

27% risk of comorbid drug/alcohol use disorders

60% comorbidity with anxiety disorders

Prevalence = 17% females: 25-30% males: 12-15%

US teenage girls ~16% 4-8% US children

significant upward trend + earlier onset since WWII

Bipolar disorder

- cycles between periods of depression and mania

Mania: euphoria inflated self-esteem sleeplessness racing thoughts psychosis talkativeness distractibility hyperactivity reckless behavior

- begins & ends more suddenly than depressive phase
- episode duration varies (days to months)

- high rate of social dysfunction
- 19% mortality through suicide (30% risk of attempts = 6X prevalence)
- 61% comorbidity with drug/alcohol use disorders

Prevalence: 3-4% same in males and females

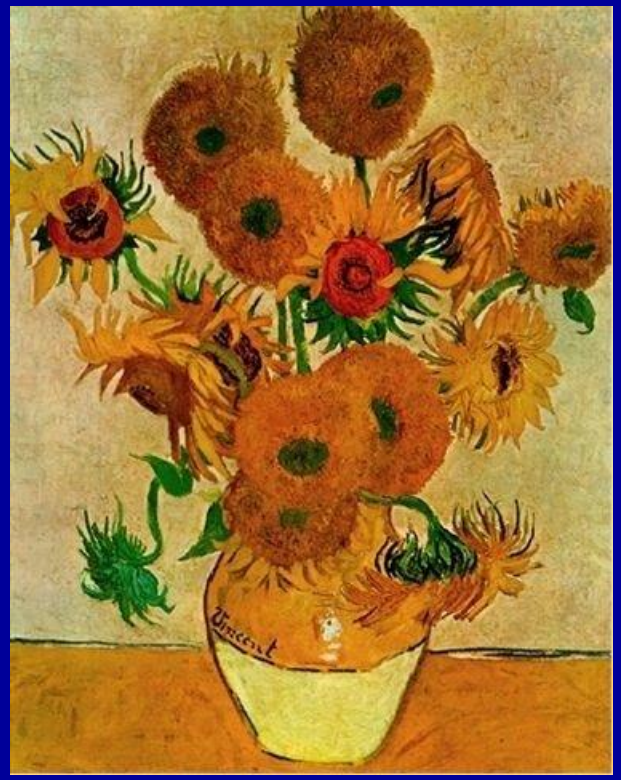
Main risk period: 16-25 years median age of onset 20 years

Other comorbidity risks (for both depression and bipolar disorder) :

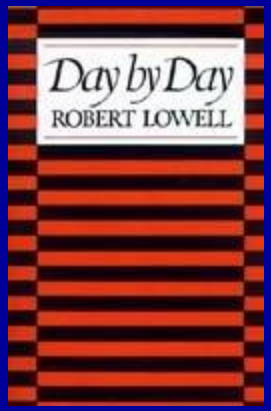
anxiety, panic disorders personality disorders

Among those thought to have suffered from bipolar disorder:

Schumann Isaac Newton Robert Lowell Beethoven Edgar Allen Poe Van Gogh Charlie Parker Graham Greene Edvard Munch Virginia Woolf William Blake Jackson Pollack


Vincent


Ludwig van Beethoven
Streichquartett · String Quartet, Op. 131
Wiener Philharmoniker · Vienna Philharmonic
Leonard Bernstein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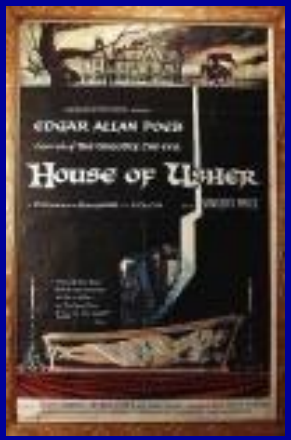
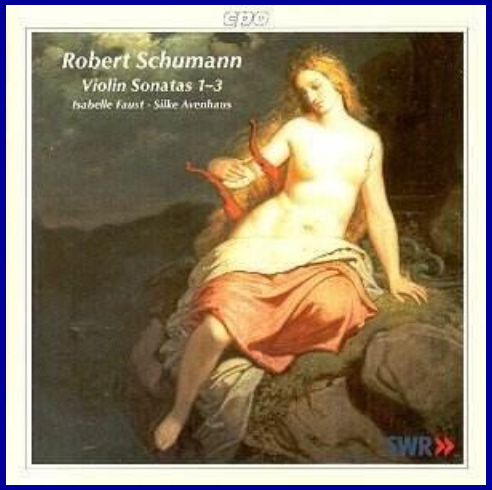
ROBERT LOWELL


EDGAR ALLAN POE
House of Usher


VIRGINIA WOOLF
MOMENTS OF BEING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Isabelle Faust · Silke Avenhaus
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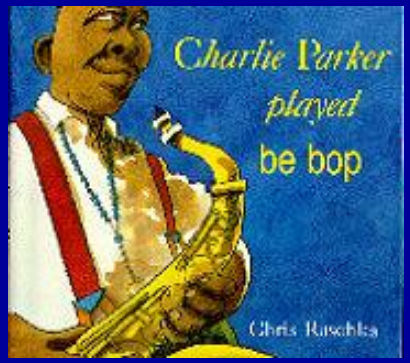
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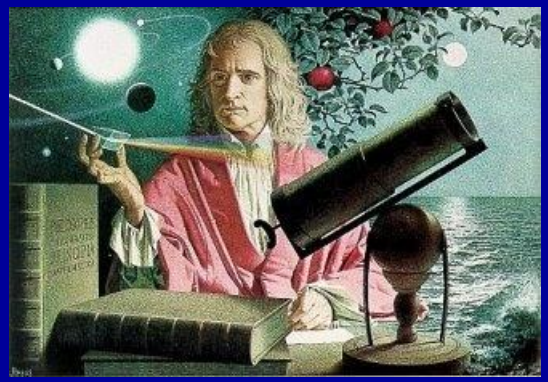
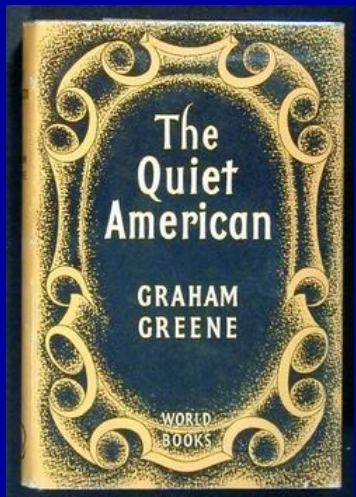
Chris Raschka




The Quiet American
GRAHAM GREENE
WORLD BOOKS

Molecular Psychiatry (2013) 18, 190–194

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ORIGINAL ARTICLE

Is bipolar disorder more common in highly intelligent people? A cohort study of a million men

CR Gale[1,2], GD Batty[2,3], AM McIntosh[4], DJ Porteous[2,5], IJ Deary[2] and F Rasmussen[6]

Anecdotal and biographical reports have long suggested that bipolar disorder is more common in people with exceptional cognitive or creative ability. Epidemiological evidence for such a link is sparse. We investigated the relationship between intelligence and subsequent risk of hospitalisation for bipolar disorder in a prospective cohort study of 1 049 607 Swedish men. Intelligence was measured on conscription for military service at a mean age of 18.3 years and data on psychiatric hospital admissions over a mean follow-up period of 22.6 years was obtained from national records. Risk of hospitalisation with any form of bipolar disorder fell in a stepwise manner as intelligence increased (P for linear trend <0.0001). However, when we restricted analyses to men with no psychiatric comorbidity, there was a 'reversed-J' shaped association: men with the lowest intelligence had the greatest risk of being admitted with pure bipolar disorder, but risk was also elevated among men with the highest intelligence (P for quadratic trend $=0.03$), primarily in those with the highest verbal (P for quadratic trend $=0.009$) or technical ability (P for quadratic trend <0.0001). At least in men, high intelligence may indeed be a risk factor for bipolar disorder, but only in the minority of cases who have the disorder in a pure form with no psychiatric comorbidity.

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Keywords: bipolar disorder; cognitive ability; comorbidity; intelligence

INTRODUCTION

The idea that genius and madness are linked dates back at least as far as the ancient Greeks. Anecdotal and biographical reports suggest that the extreme mood swings of elation and despair characteristic of bipolar disorder (previously known as manic depression) are more common in individuals with exceptional cognitive and creative ability.[1,2] Epidemiological evidence for this link is sparse. One study found that children with high IQ scores were more likely to be diagnosed with mania in adulthood than less bright peers, but there were only eight cases of mania, too few to be certain of the accuracy of this finding.[3] Another indication that exceptionally bright people may be at risk of bipolar disorder comes from findings that boys with very high or very low school grades were both more likely than those with average performance to be hospitalised with bipolar disorder as adults;[4] whether these associations are driven primarily by intelligence or by other factors that influence educational attainment is unclear. No association was found between intelligence and subsequent hospitalisation with bipolar disorder in a study of 50 000 men, but the study may have lacked the statistical power to detect an association.[5]

Bipolar disorder is uncommon in the general population, as is very high intelligence, so studying very large numbers of people is necessary for reliable detection of any association between the two. We used data on over a million Swedish men to investigate the relationship between intelligence and subsequent hospitalisation for bipolar disorder. People with higher intelligence have a lower risk of some mental disorders, including schizophrenia, non-affective psychoses, major depression, neurotic and substance use disorders.[6,7] We hypothesised that, if men with exceptional intelligence do have an increased risk of bipolar disorder, it will be bipolar disorder in its pure form with no psychiatric comorbidity.

MATERIALS AND METHODS

Study participants and record-linkage of registers

The record linkage methods used to generate this cohort study have been reported previously.[8] In brief, the cohort comprises all non-adopted men born in Sweden from 1950 to 1976 for whom both biological parents could be identified in the Multi-Generation Register. Using unique personal identification numbers we linked the Multi-Generation Register with the Military Service Conscription Register, Population and Housing Censuses records, the Cause of Death Register and the National Hospital Discharge Register. Study approval was obtained from the Regional Ethics Committee, Stockholm.

Conscription examination

The military service conscription examination involves a structured, standard medical assessment of physical and mental health, and intelligence. During the years covered by this study, the law required this examination; only men of foreign citizenship or those with severe disability were excused. This dataset covers examinations from 15 September 1969 to 31 December 1994, after which testing procedures used to assess intelligence changed. Intelligence was measured at a mean age of 18.3 years using four written

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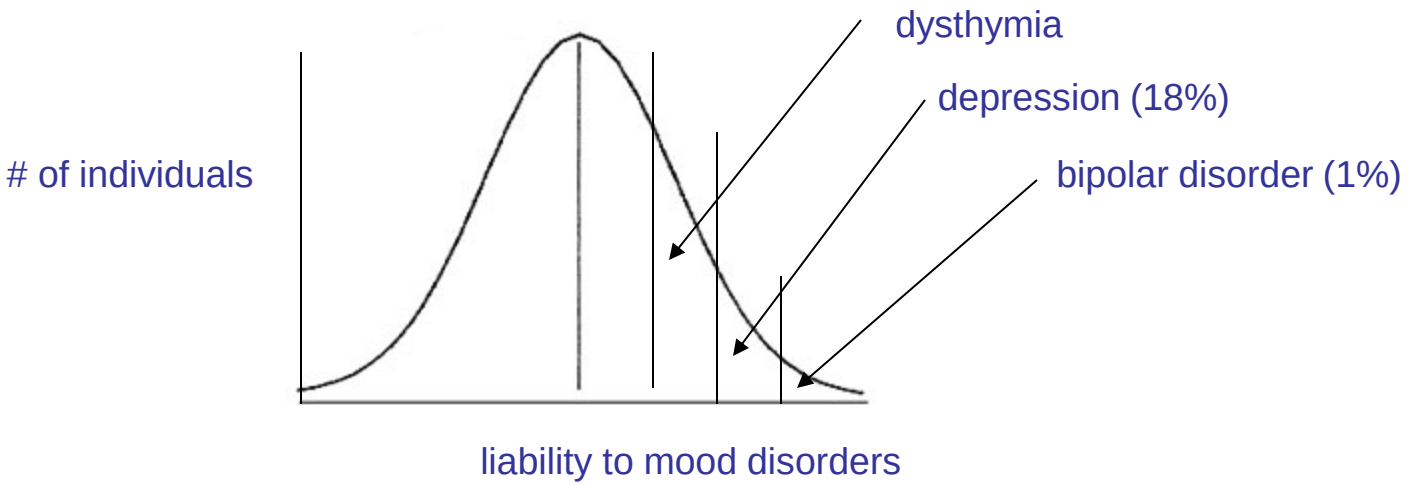
Family studies on mood disorders

Review of many studies (McGuffin & Katz, 1986):

	Severe depression	Bipolar disorder
First degree relatives	9%	9%
Unrelated (prevalence)	3%	1%
Relative with bipolar	14%	
Relative with depression		1%

More recent studies put 1st degree relative risk at 11-16% for bipolar, 67% risk if both parents affected

Evidence points to liability-threshold model for mood characteristics:



- continuum for mood disorders replaces ‘category’ classification (reactive, endogenous)
- more severe, earlier onset, more recurrent forms show higher heritability
- late onset (after age 40) depression is much less heritable
- response to drug-therapy runs in families

response to lithium for bipolar strongly familial

indicates genetic heterogeneity: different families have different risk alleles

Twin studies

		Depression	Bipolar disorder
Concordances	MZ	43%	55%
	DZ	28%	7%

confirms evidence from family studies for genetic influence

Liability-threshold model-fitting:

Depression heritability = 37%, no shared e

Bipolar heritability = 80%, no shared e

More severe depression, twin study indicates heritability of 70%

- to better estimate variance components, need some measure of phenotype:

Kendler et al (1992)

female twins population-based sample individual clinical interviews to get symptom counts as measure of disorder

In this study: lifetime prevalence of mood disorder = 29-33% (DSMIII-R)

For depressive symptoms	N(pairs)	Correlation (tetrachoric)
MZ	590	0.44
DZ	440	0.19

Sources of variance: additive gene effects 42%

non-shared environment 58%

no evidence for shared environment

Liability threshold model, heritabilities - supported by small adoption studies in bipolar, some depression studies

Environmental influences

- prolonged or intense stress has physiologically deleterious effects on the brain
- effects especially pronounced in hippocampus
- neuronal atrophy, neurotoxicity, loss of plasticity, downregulated neurogenesis - reversed by anti-depressant treatments
- linked to elevated levels of glucocorticoids

- genetic risk alleles likely increase response to stress and increase neural damage in brain

eg. genes for neurotrophic factors – regulate neurogenesis in hippocampus

BDNF gene expression affected by corticosterone levels (stress)

has antidepressant-like activity

met allele carriers – smaller hippocampal volume

anti-depressant admin. changes expression of BDNF gene

Endophenotypes for mood disorders

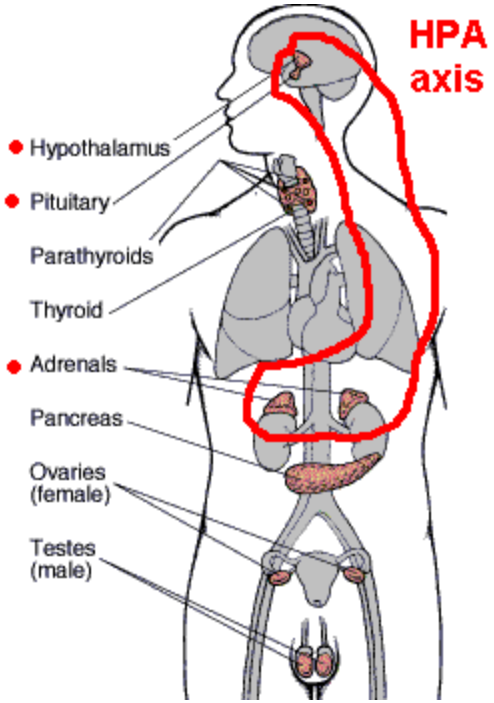
Gray-matter reductions in amygdala

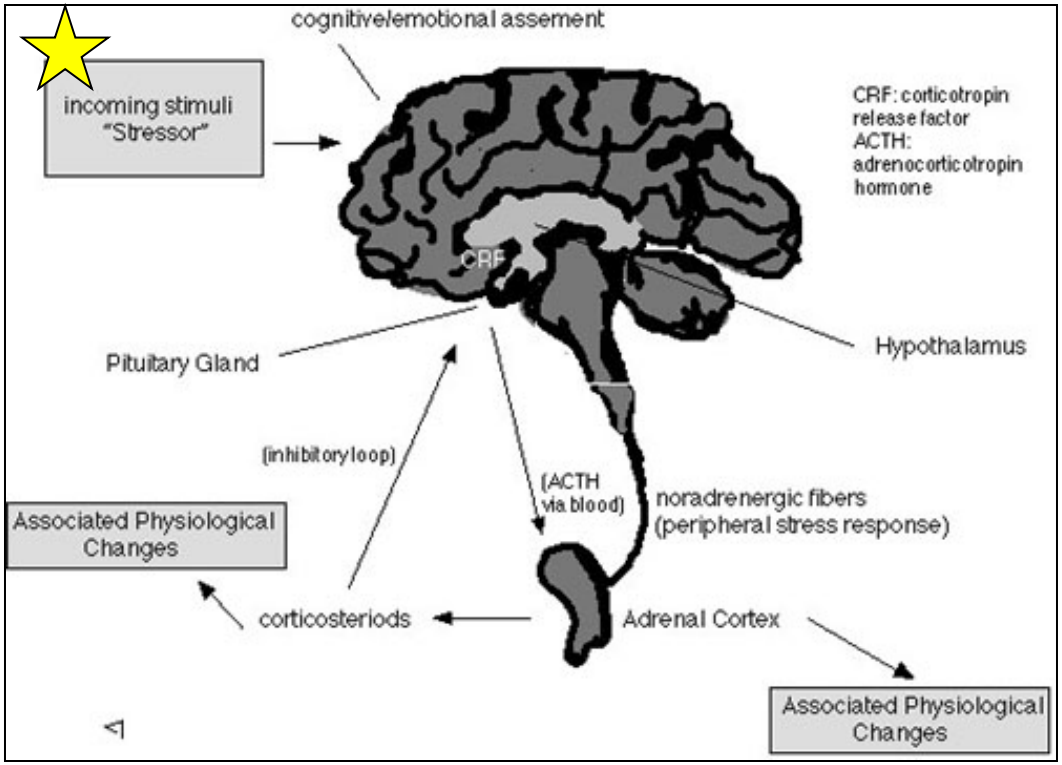
Reduced hippocampus volume

evidence shows antidepressants increase hippocampal neurogenesis by activating glucocorticoid receptors

Abnormalities in regulation of hypothalamus/pituitary/adrenal axis

major role of corticotropin-releasing factor (CRF) (maybe not just from hypothalamus but amygdala also)





Finding genes for mood disorders

multiple genetic loci of very small effect

Most success so far for genes for bipolar I - larger effect, replicated

rare dominant, chr 1 - increases risk x10 pedigree linkage

ion channel genes CACNA1C ANK3

BDNF alleles involved in hippocampus volume

neuregulin, dysbindin genes associated with both SCZ and BIP

DGKH a key protein in the lithium-sensitive phosphatidyl inositol pathway .

Still only ~26% of genetic variation accounted for

Multivariate analyses

reveal familiality and co-occurrences of both SCZ and BIP symptoms (not possible to have both disorders in DSMIV)

+ overlap between genes for bipolar and schizophrenia = 40%

indicates some shared etiology and genetic causes

Neurocan gene (NCAN)

- genome–wide significant association with BIP (2×10^{-9})
- OR = 1.17 so very small individual effect
- similar significant but small effect size in SCZ
- gene product is a proteoglycan, found in extracellular matrix, involved in cell adhesion, migration expressed in brain
- associated with mania

factor analysis of mania scores for SCZ, BIP, MDD

endophenotype: ‘overactivity’ – common to all 3 disorders

NCAN knock-out mouse – possible model for mania

- lower prepulse inhibition
- treatment with lithium raises level of prepulse inhibition

Open

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ORIGINAL ARTICLE

Genome-wide association analysis of copy number variation in recurrent depressive disorder

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Large, rare copy number variants (CNVs) have been implicated in a variety of psychiatric disorders, but the role of CNVs in recurrent depression is unclear. We performed a genome-wide analysis of large, rare CNVs in 3106 cases of recurrent depression, 459 controls screened for lifetime-absence of psychiatric disorder and 5619 unscreened controls from phase 2 of the Wellcome Trust Case Control Consortium (WTCCC2). We compared the frequency of cases with CNVs against the frequency observed in each control group, analysing CNVs over the whole genome, genic, intergenic, intronic and exonic regions. We found that deletion CNVs were associated with recurrent depression, whereas duplications were not. The effect was significant when comparing cases with WTCCC2 controls ($P=7.7\times10^{-6}$, odds ratio (OR) =1.25 (95% confidence interval (CI) 1.13–1.37)) and to screened controls ($P=5.6\times10^{-4}$, OR=1.52 (95% CI 1.20–1.93). Further analysis showed that CNVs deleting protein coding regions were largely responsible for the association. Within an analysis of regions previously implicated in schizophrenia, we found an overall enrichment of CNVs in our cases when compared with screened controls ($P=0.019$). We observe an ordered increase of samples with deletion CNVs, with the lowest proportion seen in screened controls, the next highest in unscreened controls and the highest in cases. This may suggest that the absence of deletion CNVs, especially in genes, is associated with resilience to recurrent depression.
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Keywords: CNVs; depression; GWAS

Introduction

Recurrent depressive disorder is a common psychiatric disorder associated with high morbidity, high economic burden and high rates of completed suicide.[1–3] Depressive disorder is heritable, with recurrent and severe types being substantially so,[4,5] but the specific genes involved are not known. As recurrent depression is associated with increased mortality at a young age,[3] it is logical to expect that some of the genetic contribution to the disorder may be explained by rare genomic variants operating under negative selection pressure.[6]

Genome-wide association studies of single nucleotide polymorphisms have been inconsistent in

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EXPERT REVIEW

Pathological parainflammation and endoplasmic reticulum stress in depression: potential translational targets through the CNS insulin, klotho and PPAR-γ systems

PW Gold[1], J Licinio[2] and MG Pavlatou[1]

Major depression and bipolar disorder are heterogeneous conditions in which there can be dysregulation of (1) the stress system response, (2) its capacity for counterregulation after danger has passed and (3) the phase in which damaging molecules generated by the stress response are effectively neutralized. The response to stress and depressed mood share common circuitries and mediators, and each sets into motion not only similar affective and cognitive changes, but also similar systemic manifestations. We focus here on two highly interrelated processes, parainflammation and endoplasmic reticulum (ER) stress, each of which can potentially interfere with all phases of a normal stress response in affective illness, including adaptive neuroplastic changes and the ability to generate neural stem cells. Parainflammation is an adaptive response of the innate immune system that occurs in the context of stressors to which we were not exposed during our early evolution, including overfeeding, underactivity, aging, artificial lighting and novel foodstuffs and drugs. We postulate that humans were not exposed through evolution to the current level of acute or chronic social stressors, and hence, that major depressive illness is associated with a parainflammatory state. ER stress refers to a complex program set into motion when the ER is challenged by the production or persistence of more proteins than it can effectively fold. If the ER response is overwhelmed, substantial amounts of calcium are released into the cytoplasm, leading to apoptosis. Parainflammation and ER stress generally occur simultaneously. We discuss three highly interrelated mediators that can effectively decrease parainflammation and ER stress, namely the central insulin, klotho and peroxisome proliferator-activated receptor-γ (PPAR-γ) systems and propose that these systems may represent conceptually novel therapeutic targets for the amelioration of the affective, cognitive and systemic manifestations of major depressive disorder.

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Keywords: depression; endoplasmic reticulum stress; parainflammation; translational

Major depression is a common and complex disorder of gene–environment interactions, which now represents the major burden of nonfatal disease in several countries, including Australia. In developed countries, major depression represents the second greatest burden of disease overall, and the fourth worldwide. As the outcome of the widespread impact of depression, antidepressants are now the second most dispensed drug class in the United States, second only to analgesics, which include prescription-free drugs such as aspirin and acetaminophen. Despite immense research for over 60 years, the causes of depression remain unknown and current therapeutic approaches are largely based on hypotheses that are over 40 years old. We further develop here a novel conceptual framework for the underlying biology of the affective, cognitive and systemic manifestation of major depressive disorder (MDD), with the potential to open up new translational pathways for therapeutics.

DEPRESSION AS A DYSREGULATION OF THE STRESS SYSTEM

In a two-part series published in the *New England Journal of Medicine* in 1988, we presented the concept that major depression represents a dysregulation of the stress system in response to a predisposing, stressful environment.[1,2] Many studies document that stress precipitates major depression and significantly influences its severity and natural history.[3–5] We also know that the clinical manifestations and neurobiology of the stress response and affective syndromes such as melancholic depression are very similar, both in their behavioral phenotypes and in their systemic manifestations.[1,2]

THE STRESS RESPONSE

The stress response consists of a series of coordinated behavioral and physiological manifestations that promote survival in threatening situations. Anxiety is a foremost feature. The brain has evolved an abundant circuitry for generating anxiety and for the conscious experience of fear. Anxiety and fear-related behaviors are necessary to promote survival during life-threatening situations. Their residues are stored as emotional memories encoded in the amygdala and hippocampus and emerge reflexively during threatening situations, including exposure to social stressors.[6,7] Cognitive programs shift from those that address complex, sequence-dependent and integrative processes to those that are acquired during previous bouts with danger (reviewed in Gold and Chrousos[8]). These are encoded to emerge automatically in subsequent life-threatening situations,

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ORIGINAL ARTICLE

Increased vulnerability of the brain norepinephrine system of females to corticotropin-releasing factor overexpression

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Stress-related psychiatric disorders are more prevalent in women than men. As hypersecretion of the stress neuromediator, corticotropin-releasing factor (CRF) has been implicated in these disorders, sex differences in CRF sensitivity could underlie this disparity. Hyperarousal is a core symptom that is shared by stress-related disorders and this has been attributed to CRF regulation of the locus ceruleus (LC)-norepinephrine arousal system. We recently identified sex differences in CRF_1 receptor (CRF_1) signaling and trafficking that render LC neurons of female rats more sensitive to CRF and potentially less able to adapt to excess CRF compared with male rats. The present study used a genetic model of CRF overexpression to test the hypothesis that females would be more vulnerable to LC dysregulation by conditions of excess CRF. In both male and female CRF overexpressing (CRF-OE) mice, the LC was more densely innervated by CRF compared with wild-type controls. Despite the equally dense CRF innervation of the LC in male and female CRF-OE mice, LC discharge rates recorded in slices *in vitro* were selectively elevated in female CRF-OE mice. Immunoelectron microscopy revealed that this sex difference resulted from differential CRF_1 trafficking. In male CRF-OE mice, CRF_1 immunolabeling was prominent in the cytoplasm of LC neurons, indicative of internalization, a process that would protect cells from excessive CRF. However, in female CRF-OE mice, CRF_1 labeling was more prominent on the plasma membrane, suggesting that the compensatory response of internalization was compromised. Together, the findings suggest that the LC-norepinephrine system of females will be particularly affected by conditions resulting in elevated CRF because of differences in receptor trafficking. As excessive LC activation has been implicated in the arousal components of stress-related psychiatric disorders, this may be a cellular mechanism that contributes to the increased incidence of these disorders in females.

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Keywords: corticotropin-releasing hormone; locus ceruleus; receptor trafficking; sex difference; stress

INTRODUCTION

Stress-related psychiatric disorders, such as depression and post-traumatic stress disorder (PTSD), affect ~20% of the population.[1,2] Women are twice as likely to be affected as men.[3–5] This disparity may reflect sex differences in mediators underlying the stress response. For example, estrogen positively regulates the gene for corticotropin-releasing factor (CRF), the primary mediator of the stress response and as a consequence, hypothalamic-pituitary adrenal axis activity.[6–8] Recently, we identified sex differences in the postsynaptic response to CRF that could render females more sensitive to stress and less able to adapt to chronic stressors.[9]

CRF elicits adrenocorticotropin release in response to stress.[10] CRF also regulates biogenic amine systems during stress, including the locus ceruleus (LC)-norepinephrine system.[11–13] CRF activation of the LC initiates arousal and is thought to alter attention in response to stress.[11,14–16] Although this is part of an adaptive cognitive response to stress, dysregulation of the LC-norepinephrine system by excessive CRF has been proposed to occur in pathological conditions and to underlie the hyperarousal that characterizes stress-related psychopathology.[17–20]

LC neurons of female rats are more sensitive to stress and CRF.[21] We recently demonstrated that this results from enhanced coupling between the CRF_1 receptor (CRF_1) and the Gs receptor-binding protein through which it signals.[9] Additionally, stress-induced association of CRF_1 with βarrestin2 and subsequent internalization into LC neurons was compromised in female rats.[9] This could diminish the ability to adapt to high levels of CRF as might be present with chronic stress. Together, these sex differences in CRF_1 function could contribute to the higher incidence of stress-related disorders in females, particularly those characterized by hyperarousal.

Sex differences in the function of the LC system would be most prominent during conditions of excessive CRF, as has been proposed to occur in depression and PTSD.[19,20,22–26] This can be modeled with CRF-overexpressing (CRF-OE) mice.[27–30] The best characterized CRF-OE line is a transgenic in which CRF expression is under control of the metallothionein promoter (mMT-1).[27] In these mice, CRF is elevated in brain neurons in most regions that normally express CRF. This contrasts with conditional models in which CRF is expressed ubiquitously in brain or is limited to forebrain neurons where it is not typically expressed.[29,30] Given the relative restriction of CRF-overexpression to brain neurons that typically express CRF, this study used the transgenic CRF-OE line to best mimic CRF overexpression that would be expected to occur in stress-related psychiatric disorders. In these mice, LC neuronal discharge characteristics and morphology were

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ORIGINAL ARTICLE

Socioeconomic position predicts long-term depression trajectory: a 13-year follow-up of the GAZEL cohort study

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Individuals with low socioeconomic position have high rates of depression; however, it is not clear whether this reflects higher incidence or longer persistence of disorder. Past research focused on high-risk samples, and risk factors of long-term depression in the population are less well known. Our aim was to test the hypothesis that socioeconomic position predicts depression trajectory over 13 years of follow-up in a community sample. We studied 12 650 individuals participating in the French GAZEL study. Depression was assessed by the Center for Epidemiological Studies-Depression scale in 1996, 1999, 2002, 2005 and 2008. These five assessments served to estimate longitudinal depression trajectories (no depression, decreasing depression, intermediate/increasing depression, persistent depression). Socioeconomic position was measured by occupational grade. Covariates included year of birth, marital status, tobacco smoking, alcohol consumption, body mass index, negative life events and preexisting psychological and non-psychological health problems. Data were analyzed using multinomial regression, separately in men and women. Overall, participants in intermediate and low occupational grades were significantly more likely than those in high grades to have an unfavorable depression trajectory and to experience persistent depression (age-adjusted ORs: respectively 1.40, 95% confidence interval (CI) 1.16–1.70 and 2.65, 95% CI 2.04–3.45 in men, 2.48, 95% CI 1.36–4.54 and 4.53, 95% CI 2.38–8.63 in women). In multivariate models, the socioeconomic gradient in long-term depression decreased by 21–59% in men and women. Long-term depression trajectories appear to follow a socioeconomic gradient; therefore, efforts aiming to reduce the burden of depression should address the needs of the whole population rather than exclusively focus on high-risk groups.
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Keywords: depression; longitudinal cohort study; occupational grade; socioeconomic gradient; socioeconomic position

Introduction

Each year, 3–7% of individuals living in industrialized countries suffer from depression; 10–15% are affected over the course of their lifetime.[1,2] Among people who have depression at a particular point in time, an estimated 35–50% will experience symptoms that are recurrent or persistent[3,4] and another 20% may have residual symptoms that impair daily activities and increase the long-term risk of physical health, social and economic difficulties.[5] Identifying factors that predict depression trajectories over time is important from both a clinical and a public health perspective.

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Previous research suggests that depression is especially likely to occur among individuals who have low socioeconomic position, as measured by educational level, occupational grade or income.[6] However, it is not clear whether socioeconomic position predicts depression trajectories over time. First, with few exceptions,[7–11] previous studies reporting socioeconomic inequalities with regard to depression persistence have been based on high-risk or clinical samples,[12–15] which may not be sufficiently varied to contrast groups with different levels of resources.[6,16] Second, prior investigations based on community samples were characterized by limited follow-up (up to 3 years),[7,8,10] high attrition (13% per year over a 7-year follow-up)[9] or followed individuals who were depressed at baseline.[11] Growing evidence suggests that in the population, most health outcomes follow a socioeconomic gradient,[17] and there is need for additional data on determinants of depression trajectories in broad samples. Third, although depression rates and the role of

Gene / environment interaction produces depression

environment - response to life events

– increased number of stressful life events is associated with increased risk for depression (OR=1.41)

- but, life events cause depression in some but not others, depending on genotype

Can we show the interaction with a particular genotype?

genotype - 5HTTLPR (serotonin transporter promotor region)

– functional polymorphism associated with gray matter reductions, possible association to depression

Caspi et al (Science, July, 2003)

identified stressful life events known to increase risk of depression
threat loss humiliation defeat

- reaction to the life events depends on the HTTLPR genotype of the individual?

chr 17 ~50% Causasians have risk-allele (short allele)

However
– recent meta-analysis (Risch et al, JAMA,2009)
- looked at results of 14 studies well-designed to show this g x e
- no evidence for main effect of genotype on depression
- no evidence for g x e in either sex

New possible treatments?

There is a chemical that

produces remission within 80 mins

one dose effective for 7-10 days

reduces suicidal ideation

works in treatment resistant patients

What is it?

A low dose of ketamine (NMDA R antagonist)

- new treatments being developed and tested based on action of ketamine, glutamate system

Also: LSD for alcohol addiction (1 dose lowers use for 3-6 months)

psilocybin for nicotine addiction

MDMA (ecstasy) for PTSD, major depression

Co-occurrence of disorders (Comorbidity)

- having one disorder results in 50% chance of also having another disorder within 12 months
- more serious the disorder, the higher the comorbidity

Examples;

Anxiety disorders:

GAD, panic, phobias, OCD, PTSD – substantial genetic overlap, differences largely nonshared e, no shared e

Internalizing: Anxiety and depression:

genetic correlation = 1 replicated, lifetime estimates and one-year prevalences, 23 twin,12 family studies

Externalizing: alcohol & other drug dependence, adult antisocial behavior, conduct disorder - substantial genetic overlap

Hopefully, recognition of this in DSMV

Diffusion tensor imaging (DTI)

- maps diffusion of water through brain fibers
- shows major fiber pathways, patterns of connectivity
- white matter anomalies seen in developmental (autism), degenerative diseases (AD, mild cognitive impairment), and in psychopathologies (SCZ, BIP, ADHD)
- neuropsychiatric treatments produce changes in DTI measures
- may make a good new endophenotype (performed in MRI scanner)

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HYPOTHESIS

The evolutionary significance of depression in Pathogen Host Defense (PATHOS-D)

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Given the manifold ways that depression impairs Darwinian fitness, the persistence in the human genome of risk alleles for the disorder remains a much debated mystery. Evolutionary theories that view depressive symptoms as adaptive fail to provide parsimonious explanations for why even mild depressive symptoms impair fitness-relevant social functioning, whereas theories that suggest that depression is maladaptive fail to account for the high prevalence of depression risk alleles in human populations. These limitations warrant novel explanations for the origin and persistence of depression risk alleles. Accordingly, studies on risk alleles for depression were identified using PubMed and Ovid MEDLINE to examine data supporting the hypothesis that risk alleles for depression originated and have been retained in the human genome because these alleles promote pathogen host defense, which includes an integrated suite of immunological and behavioral responses to infection. Depression risk alleles identified by both candidate gene and genome-wide association study (GWAS) methodologies were found to be regularly associated with immune responses to infection that were likely to enhance survival in the ancestral environment. Moreover, data support the role of specific depressive symptoms in pathogen host defense including hyperthermia, reduced bodily iron stores, conservation/withdrawal behavior, hypervigilance and anorexia. By shifting the adaptive context of depression risk alleles from relations with conspecifics to relations with the microbial world, the Pathogen Host Defense (PATHOS-D) hypothesis provides a novel explanation for how depression can be nonadaptive in the social realm, whereas its risk alleles are nonetheless represented at prevalence rates that bespeak an adaptive function.
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Keywords: major depression; evolution; immune; inflammation; infection; genetic

Introduction

Major depression is so detrimental to survival and reproduction that it is hard to understand why allelic variants that promote the disorder have not been culled from the human genome, why in fact—far from being culled—genes that promote depression are so common and numerous and appear to have actually increased in prevalence during recent human evolution.[1] To address this issue, we have developed a novel theoretical framework positing that risk alleles for depression originated and have been largely retained in the human genome because these alleles encode for an integrated suite of immunological and behavioral responses that promote host defense against pathogens. This enhanced pathogen defense is accomplished primarily via heightened innate immune system activation, which results in reduced death from infectious causes,[2–6] especially in infancy when selection pressure from infection is strongest,[6] and the adaptive immune system is not yet fully operational.[6–8] A vast literature has associated depressive symptoms and/or major depressive disorder (MDD) with increased innate immune inflammatory responses,[10] with meta-analyses reporting the most consistent findings for increased plasma concentrations of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), C-reactive protein and haptoglobin.[11–13] Recent longitudinal studies extend these cross-sectional observations by reporting that increased inflammatory markers in nondepressed individuals predict the later development of depression.[14–16] Because infection has been the primary cause of early mortality and hence reproductive failure across human evolution,[6,17–21] it would be expected that if depressive symptoms were an integral part of a heightened immunological response, allelic variants that support this response would have undergone strong positive selection pressure and thus would be both numerous and prevalent, as they appear to be. However, because

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