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Old Obstacles on New Horizons: The Challenge of Implementing Gene X Environment Discoveries in Schizophrenia Research

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1. Introduction

Genetics and Social Sciences are divergent disciplines for whom it is customary to compete to explain the greater part of Schizophrenia risk ¹. These days, a convincing case can be made for the prospective public health value of either discipline ^{2,3}. However the practical implementation of such knowledge continues to prove challenging for either field alone: From a genetic perspective, progress was traditionally hindered by the inconsistent nature of discoveries made in the pre-GWAS (Genome-wide Association Study) era. It is now held back by the fact that the heritability attributed to this disorder remains largely impermeable to GWAS and other genomic approaches.

Socio-environmental research, on the other hand, has not progressed to the point of being able to pinpoint the precise origins of the high attributable risk fractions repeatedly encountered ².

However ongoing progress on two fronts is fuelling hopes that a successful marriage of the two fields will benefit both the rate and the integrity of new discoveries, so that clinical interventions can eventually be targeted to patient sub-groups on the basis of their combined genetic and environmental risk profile:

- i. Firstly, the credibility of Schizophrenia genetics is benefiting from a recent upswing in the generation of verifiable new findings. This has led to a palpable mood change within the psychiatric genetics community ⁴.
- ii. Secondly, it is anticipated that social science research will benefit from an unprecedented program of investment that will stimulate the emergence of newer methodologies designed to improve the resolution with which social risk factors are measured ^{5,6}.

There are high hopes that the formal integration of these two fields will help to invigorate the search for tailored clinical interventions, whether they be therapeutic or prophylactic in nature. Thus it seems an opportune time to consider the potential obstacles that lie ahead for Schizophrenia research in the newly revitalised era of translational research. We do this by

taking a fresh look through a retrospective lens, at the historical stumbling blocks for the GxE field. We discuss some of the new opportunities (horizons) at the disposal of GxE researchers designed to circumvent them. Some of these hail from recent advances in biobanking, meanwhile new bioinformatic initiatives are helping to transform electronic clinical databases into similarly powerful research tools.

We also highlight the potential pitfalls of an over-regulated clinical trial environment and the detrimental consequences this may eventually have on the pipeline for new drugs. Currently there are fears that an over-burdensome European regulatory legislature is responsible for the recent efflux of companies away from the European clinical trial market. This may create an unwanted bottleneck (or worse still, a precipice) within the new and fully-functional formal framework designed to shepherd only the most robust GxE discoveries into the clinic. We begin this chapter with a brief review of some important concepts central to a discussion on Gene-Environment inter-dependency.

2. The enigma surrounding heritability

Heritability is defined as the proportion of phenotypic variance due to genetic variance. The concept of Schizophrenia as a heritable disorder was once considered to be controversial, though this is no longer the case. From a scientific perspective it is well worth knowing beforehand that a phenotype of potential interest is heritable enough to merit the effort of dissecting genetically. Thus, establishing that this is the case, is a prerequisite first step in genetic research.

Formal estimates of heritability can be obtained through a number of different methods. The archetypal approach uses twins ⁷. Twin studies suggest that susceptibility to Schizophrenia is predominantly a genetic phenomenon that accounts for 65-80% of overall risk ^{7,8}. But that upper estimate is likely to understate the true importance of the environment. Even highly penetrant genetic risk factors (such as a syndromic deletion on chromosome 22q11), are not always sufficient to elicit Schizophrenia on their own ⁹. This is confirmed by the fact that pathogenic genetic anomalies are often harboured by asymptomatic controls, as well as cases ¹⁰. This suggests that the underlying risk conferred is heavily mitigated by the environment and other background genetic modifiers of main effects.

Heritability studies estimate that the environmental contribution to Schizophrenia is between 15-35% of the phenotypic variance. The issue of which science explains the greater part of risk is contentious; social science research bases its own claims of dominance on larger explained effects, and also recent calculations which suggest that the burden of cases occurring in the general population could be averted through social interventions ². In truth, methodological biases in both fields mean attempting to delineate between the effects of genes and environment is a somewhat arbitrary exercise. This is because classical approaches to heritability estimation do not automatically factor-in the dependency which may occur between genes and environment. Meanwhile, one all-important confounder not accounted for by the social risk liability models of Kirkbride et al ², is a family history of psychiatric disorder, (a proxy for genetic influence). It is important to keep in mind that these methodological limitations mean that a disorder caused by GxE will be attributed to Genes in a twin study and Environment in an epidemiological study.

This ambiguity probably explains why heritability estimates for Schizophrenia have historically been so variable; the value of each estimate is affected by parameters defined by the population under study, and also the degree to which characteristics such as gender, age, and environment exposure profile have been averaged-over ¹¹. Therefore it comes as no surprise that genetic epidemiology research in Psychiatry is fast becoming preoccupied with redefining heritability itself ¹¹. Some principle areas of interest emerging from such work include;

- the stability of heritability over time
- genetic determination of sensitivity to exposure

Twin studies and other methods impose a fixed-point approximation of heritability. But this fails to adequately capture the inherent mobility of heritability over time. Evidence for this drift comes from longitudinal studies of both Substance Misuse and Depression. These demonstrate a tendency for heritability to increase across the developmental period between adolescence and adulthood ¹², and also with later stages of decline ¹³. These studies show that the initiation of cannabis use is predominantly an environmental phenomenon, although genetic influences become increasingly important as the level of usage progresses towards substance abuse and drug dependency ¹⁴. In extreme scenarios within polygenic disorders, heritability may reach a higher level during earlier neuro-developmental stages. Such cases tend to result in earlier onset. For Schizophrenia, the earliest cases are known to occur during childhood ¹⁵.

3. Multifactorial risk factors for Schizophrenia

Table 1 lists some of the important exposures known to affect the risk of Schizophrenia. The main origins are social, socio-economic and neuro-developmental. As well as being very common many of these risk factors are associated with large effects. Odds ratios (ORs), reflect the odds of exposure to a risk factor in cases relative to controls (expressed as a fold-difference).

Table 1. Environmental Risk factors for Schizophrenia - a non-exhaustive list

Context	Environmental Risk Factor	Recent Review	Recent meta-analysis
Social	Urban-Rural dwelling	March et al, 2008 ¹⁶	-
	Social Context - Neighbourhood effects	-	-
	Social Discrimination-Discrimination	-	Allardyce et al, 2005 ¹⁷
	Migration	Cantor-Graae and Selten, 2005 ¹⁸	DeAlberto et al, 2010 ¹⁹ Arsenault et al, 2002 ²¹ ; Henquet et al, 2005 ²² ; Moore et al, 2007 ²³
Familial	Cannabis Use	Henquet et al, 2008 ²⁰	-
	Childhood Trauma	Morgan and Fisher, 2007 ²⁴	-
	Advancing Paternal age	Miller et al, 2010 ²⁵	Miller et al 2011 ²⁶
Neurodevelopmental	Seasonal birth	Davies et al, 2003 ²⁷	Davies et al, 2003 ²⁷
	Birth defects/Obstetric complications	-	-
	Seasonal birth	-	-
Economic	Vitamin D	-	-
	Developed vs Developing Country	-	Saha et al, 2005 ²⁵
	Socio-Economic status	Cohen et al, 2008 (22)	-
Other		-	-
	Gender	-	Aleman et al, 2003 ²³
		-	McGrath et al, 2004 ²⁴

The typical effect range of the risk factors shown in table 1 typically range from 1.5 to 11. In contrast, common genetic risk factors for Schizophrenia are much smaller, typically with Odds ratios of between 1.1 – 1.4. See table 2 for a summary of genetic risk factors for Schizophrenia deriving from large-scale (genome-wide) genetic studies.

Table 2. Genetic Risk factors for Schizophrenia

Chromosome	Gene/Region	Symbol	Full Gene Name	GWAS Significance threshold	Reference	
1	1q21.1 deletion			Too rare to compute	28-36	
	1q21.1	<i>BCL9</i>	B-cell CLL/lymphoma 9	Strongly suggestive	37	
	1p21.3	<i>MIR137</i> (intron 3 of miRNA transcript)		Significant	4	
	1q24			Significant	38	
	1q32.2	<i>PLXNA2</i>	plexin A2	Strongly suggestive	39	
2	2p16.1	<i>VRK2</i>	vaccinia related kinase 2	Significant	40,41	
	2p16.3 deletion	<i>NRXN1</i>	neurexin 1	Too rare to compute	28,31-35,42-44	
	2p22.2	<i>SULT6B1</i>	sulfotransferase family, cytosolic, 6B, member 1	Strongly suggestive	45	
	2q32.1	<i>ZNF804A</i>	zinc finger protein 804A	Strongly suggestive	46-48	
	2q32.3	<i>PCGEM1</i> (non-coding RNA transcript)	(prostate-specific transcript 1	Significant	4	
	2q33.3-q34	<i>ERBB4</i>	v-erb-a erythroblastic leukemia viral oncogene homolog 4 (avian)	Strongly suggestive	49	
	2q34-q35	<i>ACSL3-KCNE4</i>	acyl-CoA synthetase long-chain family member 3	Significant	50	
	2q37	<i>CENTG2/AGAP1</i>	ArfGAP with GTPase domain, ankyrin repeat and PH domain 1	Strongly suggestive	49	
	2q37.1	<i>UGT1A1-HJURP</i> (intergenic)	Holliday junction recognition protein	Significant	50	
	2q37.3	<i>AK573765-TWIST2</i> (intergenic)	twist homolog 2 (Drosophila)	Significant	50	
	2q37.3	<i>LRRFIP1</i>	leucine rich repeat (in FLII) interacting protein 1	Significant	50	
	3p21.1	<i>PBRM1</i>	Polybromo 1	Strongly suggestive	51	
	3	3q21-q23	<i>RELN</i>	reelin	Strongly suggestive	52
		3q21-q23	<i>RBP1</i>	retinol binding protein 1, cellular	Strongly suggestive	53
		3q39 deletion			Too rare to compute	28,32,34,35,43, 54
5	5q14.1	<i>CMYA5</i>	cardiomyopathy associated 5	Strongly suggestive	55	
6	6p21	<i>ZKSCAN4</i>	zinc finger with KRAB and SCAN domains 4	Significant	56	
	6p21.3	<i>NOTCH4</i>	notch 4	Strongly suggestive	45,57	
	6p22.1	MHC region		Significant	49,57,58	
	6p22.1	<i>NKAPL</i>	NFKB activating protein-like	Significant	56	
	6p22.1	<i>PGBD1</i>	piggyBac transposable element derived 1	Significant	56,57	
	6p22.1	<i>LOC645434-NMBR</i>				
	6q21-qter	(intergenic)	neuromedin B receptor	Significant	50	
	6q23.2	<i>AH11</i>	Abelson helper integration site 1	Strongly suggestive	59	

Chromosome	Gene/Region	Symbol	Full Gene Name	GWAS Significance threshold	Reference
7	7q11.23-q21.3	<i>PCLO</i>	piccolo (presynaptic cytomatrix protein)	Strongly suggestive	60
	7q36.3 duplication	<i>VIPR2</i>	vasoactive intestinal peptide receptor 2	Too rare to compute	28,32,53,61,62
8	8p12			Significant	38
	8p21-p12	<i>NRG1</i>	neuregulin 1	Strongly suggestive	49
	8q21	<i>MMP16</i>	matrix metalloproteinase 16	Significant	4
11	8p23.2	<i>CSMD1</i>	CUB and Sushi multiple domains 1	Significant	4
		<i>NRGN</i>	neurogranin (protein kinase C substrate, RC3)	Significant	41,57
12	11q24.2	<i>CACNA1C</i>	calcium channel, voltage-dependent, L type, alpha 1C subunit	Suggestive	63
15	12p13.3 deletion			Too rare to compute	28,32,34
16	15q13.2 deletion			Too rare to compute	28,32,35
	16p11.2 duplication			Too rare to compute	28,30,31,34
17	16p13.11 duplication			Too rare to compute	32,34
18	17q12 deletion	<i>TCF4</i>	transcription factor 4	Significant	41,57
22	18q21.1				28,31,32,34,36,
	22q11.21 deletion			Too rare to compute	54
X	Xp22.3 & Yp13.3	<i>IL3RA</i>	interleukin 3 receptor, alpha (low affinity)	Strongly suggestive	64
	Xp22.32 & Yp11.3	<i>CSF2RA</i>	colony stimulating factor 2 receptor, alpha	Strongly suggestive	64

Table 2. CNVs (Copy Number Variants) are sub-microscopic deletions and duplications of DNA (typically greater than 100kb in size). SNP (Single Nucleotide Polymorphism) refers to a single subunit (base) change in the DNA sequence. *CACNA1C*, *ZNF804A*, *NRGN*, *MHC* and *PBRM1*, all overlap with Bipolar Disorder. *Genome-wide significant = $P < 5 \times 10^{-8}$; Strong significance is defined as a P value of between 5×10^{-4} and 5×10^{-8} . **Notes the pre-existence of this gene as a commonly-researched candidate in Schizophrenia research prior to GWAS. Note within table 2 the high occurrence of findings validated by more than one study. This is particularly obvious for CNVs, but is also evident for SNP variants, including those not reaching overall significance.

The effects of Environmental risk factors are on a par with those of the structural variants⁹, catalogued in Table 2, but the latter occur much too infrequently to explain the fact that Schizophrenia is common mental disorder, affecting 1% of the global population. In fact, the molecular modalities identified so far for Schizophrenia (namely copy number and common variation) currently account for no more than 3% of the total phenotypic variance of Schizophrenia⁶⁵.

The discrepancy between theoretical and observed heritability estimates has led many to speculate on possible reasons why the 'missing' component is so elusive⁶⁶. The possibilities span a wide array of plausible theories, most of which are based on the premise that the additive component of heritability is probably exaggerated. eg⁶⁷.

4. The fundamental models of gene-environment dependency

Nowadays, it is possible to examine the theory that heritability has been overstated, by testing the significance of the difference in heritability between exposure and non-exposure twin models ¹¹. This is an appropriate way to empirically test the dependency between genes and environment.

The risk factors shown in table 1, while very common, are mitigated by the genetic make-up of the individual, such that the overall effect on risk is relatively small. At a population level this means that only a small proportion of those encountering these exposures will ever go on to develop clinical symptoms. This example of inter-dependency is known as Gene-Environment interaction. Cumulatively it may have a large impact on psychosis risk at the population level.

4.1 G-E correlation (rGE)

Analytically, GxE is difficult to distinguish from gene-environment correlation (rGE), a phenomena whereby exposure to exogenous risk factors is encoded within the DNA of the individual. rGE represents the social manifestation of one's genetic heritage, and its influence on subsequent lifestyle choices. If not properly accounted for, rGE can quietly confound the apparent interaction between genes and the environment.

There are many behavioural examples of this phenomenon in the psychiatric literature (reviewed in ⁶⁸). For instance, genes can have an indirect influence on adolescent substance misuse, through a mechanism in which genes drive the selection of friends who facilitate this behaviour. In this example, peer-group choice can be redefined as a lifestyle trait with a strong genetic component ⁶⁹. An equally compelling case can be made for rGE in Depression, as there is an indication that genetic susceptibility to Depression may also partly reflect a person's tendency to experience stressful experiences, such as interpersonal and romantic difficulties ⁷⁰.

The evidence used to discuss G-E dependency in the context of Schizophrenia is drawn almost exclusively from the cannabis literature, as it is one of the most commonly investigated risk factors in GxE research. Its popularity probably reflects the relative ease with which data on this exposure may be obtained and verified, with good sensitivity and specificity. This makes it comparatively easy to derive a fairly accurate profile of exposure using retrospective assessments ^{71,72}.

While there is little in the way of direct experimental evidence to support the occurrence of rGE in Schizophrenia, it would be surprising if Schizophrenia were shown to be completely devoid of the phenomenon, given its demonstration in other areas of behavioural research ⁶⁸. Only one study has purported to show evidence of the rGE mechanism in Schizophrenia ⁷³. Meanwhile the evidence that contradicts this finding has withstood the many different experimental designs applied to re-address the same question eg. ^{21,74,75}. The most recent of these used a case-control design ⁷⁵, and also included a comparison of lifetime cannabis consumption between the siblings of cases (who have a higher genetic propensity for Schizophrenia) and healthy controls. It found

no difference between these two groups and thus does not find support a role for Schizophrenia genes in the initiation of cannabis use.

4.2 G-E interaction (GxE)

Interaction is a more solidly supported mechanism of G-E dependency in Schizophrenia, whose influence clearly extends to cannabis use. For example, early studies have suggested that familial (presumably genetic) influences on SZ risk also augment the psychotogenic effects of this drug ⁷⁶. Another study finds that the same level of familial liability is reached among cases of cannabis-induced psychosis, as that found among Schizophrenia patients; a strong indication that the enhanced responsiveness to cannabis in these hospitalised users is enabled by Schizophrenia genes ⁷⁷. Cannabis use can thus be said to advance the genetic risk of Schizophrenia onset. The same can be said of urbanicity ⁷⁸ and prenatal exposure to infection ⁷⁹, but seemingly not of obstetric complications ⁸⁰.

One drawback of the *familial liability* study design is that genetic and environmental effects cannot so easily be discerned within the construct of 'familiality', which is inferred as being predominantly genetic in origin, but which also incorporates an element of shared environmental risk. The adoption study design therefore, is a convenient way to disentangle the components of this construct, by allowing the genetic component to be assessed in isolation of shared environmental influences.

The adoption study design has been widely used for this purpose in Schizophrenia research. A recent exemplar for the approach investigated psychosis in 13,000 entrants on the Swedish National Adoption Register. Using an empirical approach, the study confirmed the relevance of early life parental employment status, parental separation and housing status to underlying Schizophrenia risk. Importantly this occurred both dependently and independently of underlying genetic liability. The synergism between genes and environment was many times greater than either additive or multiplicative risk thresholds, indicating a strong interaction. The findings were later validated in 26,000 individuals derived from the general population ⁸¹.

5. Candidate gene studies of gene-environment interaction

Currently, Gene-Environment interaction is one of a few areas of genetic research in which the candidate-gene design has had the upper hand over the more systematic approach represented by Genome-wide Association studies (GWAS). A favoured approach uses biological plausibility to guide the formulation of coherent hypotheses ⁸². This strategy has several high profile discoveries to its credit. Table 3 Lists the GxE studies performed to date in psychosis and summarises the individual outcome of each. Heterogeneity among hypotheses and methodological approaches precludes a more formal assessment of current experimental evidence (ie. by meta-analysis).

Universal acknowledgement of the GxE concept in Schizophrenia alone ^{78-81,83-86} tends to suggest that its pervasiveness across psychiatry should be on a par with the rest of nature. However the paradox of GxE in Psychiatry is that though generally acknowledged, the interactions themselves are proving difficult to individually identify.

Table 3. Studies investigating interactions between candidate susceptibility genes and candidate environmental pathogens in relation to psychosis.

Author	Sample size	Candidate G	Candidate E	Outcome Variable	Results	Statistics
Zammit et al 2011	2630 HC general population	COMT Val(158)Met	Cannabis	Self-reported psychotic experiences at age 16	No interaction	p=0.304-0.981 OR=0.83-1.10
vanWinkel et al 2011	810 SZ, 740 siblings, 419 HC	152 SNPs in 42 candidate genes	Cannabis	Psychotic disorder	Interaction with AKT1 rs2494732 only in cases	p=0.007
Ho et al 2011	235 SZ	12 tag SNPs in CBI/CNR gene	Cannabis	Brain Volume and Neurocognition in SZ	- Brain Volume: rs12720071-G-allele carriers with marijuana misuse had the smallest meanparietal WM volumes. rs7766029-C/C associated with small temporal and parietal WMvolumes. rs9450898-C/C associated with small frontal and parietalWMvolumes. - Neurocognition: CNR1 rs12720071-G-allele carriers with marijuana misuse had the worst problem solving test performance.	p<0.05 p≤0.05 p≤0.05 mean z=-1.78
Decoster et al 2011	585 SZ	BDNF Val(66)Met	Cannabis	Psychotic disorder (Age of onset)	- No BDNF x Cannabis interaction. - Significant BDNF x Cannabis x Sex interaction (females).	p=0.420; $\chi^2(1)=0.65$ p=0.023; $\chi^2(1)=5.15$
Kantrowitz et al 2009	92 SZ (33 Caucasian, 46 African-American)	COMT Val(158)Met	Cannabis	Adolescent cannabis use	No association cannabis use-COMT genotypes (African-American/Caucasians)	p=0.23/0.49; $\chi^2(2)=2.9/1.4$
Henquet et al 2009	31 psychotic disorder, 25 HC	COMT Val(158)Met	Cannabis (ESM)	Psychotic symptoms (hallucinations, delusions) in daily life (ESM)	Cannabis increased hallucinations in Val/Val carriers with high levels of psychometric psychosis liability.	p<0.001; $\beta=0.78$
Zammit et al 2007	750 SZ, 688 HC	CNR1, CHRNA7, COMT Val(158)Met	Cannabis, Tobacco	Psychotic disorder	No interaction with CNR1 or COMT genotypes.	p>0.05; OR=0.83-0.98
Henquet et al 2006	30 psychotic disorder, 12 relatives, 32 HC	COMT Val(158)Met	Cannabis	D-9-THC-induced psychotic experiences	Condition x Val/Val x Psychometric psychosis interaction.	p=0.003; $\chi^2(1)=8.86$
Caspi et al 2005	803 HC general population	COMT Val(158)Met	Cannabis	Schizophreniform disorder	Cannabis x Val/Val x Schizophreniform disorder interaction.	p=0.025; OR=10.9
Aleman et al 2011	533 HC general population	BDNF Val(66)Met	Childhood abuse and neglect	Positive and negative psychotic-like experiences	BDNF (Met/-) x childhood abuse x positive psychotic-like experiences interaction.	p=0.004; $\beta=0.27$, SE=0.10

Author	Sample size	Candidate G	Candidate E	Outcome Variable	Results	Statistics
Husted et al 2010	98 broadly defined SZ, 79 narrowly defined SZ, 86 siblings	<i>NOS1AP</i>	Childhood trauma	SZ	Narrowly defined SZ more likely to have a history of early trauma than their unaffected family members (similar results after controlling for <i>NOS1AP</i>).	OR=4.17; 95% CI=1.52, 11.44
Muntjeswerff et al 2011	742 SZ, 884 HC	<i>MTHFR 677 C>T</i>	Winter birth	SZ	No winter period x <i>MTHFR 677- T/T</i> x SZ interaction.	p=0.744; OR=0.90
Chotai et al 2003	954 UPAD, BPAD, and SZ 395 HC	<i>TPH, 5-HTTLPR and DRD4</i>	Seasonality of birth	Season of birth variations in UPAD, BPAD and SZ	- <i>TPH-A</i> allele associated with one-cyclic season variation in women controls and men with BPAD. - <i>DRD4</i> 7-repeat associated with one-cyclic season variation in SZ women. -5- <i>HTTLPR</i> s allele associated with one-cyclic season variation in men with UPAD.	p=0.05 p=0.01 p=0.01
Tochigi et al 2002	110 SZ, 493 HC	<i>HLA-A24 and A26</i>	Seasonality of birth	Association between <i>HLA-A</i> and birth-season in SZ	No association between winter birth (December-March) and <i>A24/A26</i> SZ	p=0.6/0.4; $\chi^2(1)=0.4/0.7$
Narita et al 2000	60 SZ + <i>HLA-DR1</i> , 307 SZ no <i>HLA-DR1</i>	<i>HLA-DR1</i>	Seasonality of birth	Association between <i>HLA-DR1</i> and winter birth in SZ	<i>HLA-DR1</i> associated with winter births in patients.	p=0.003; $\chi^2(1)=8.64$
Haukvik et al 2010	54 SZ, 53 HC	32 SNPs in <i>BDNF, DTNBP1, GRM3 and NRG1</i>	Obstetric Complications (OCs)	Hippocampal volume	- <i>GRM3</i> rs13242038 associated with severe OCs on hippocampal volume. -No significant interaction with SZ	$p_{\text{diagnosis} \times \text{OCs}}=0.25$ $p_{\text{diagnosis} \times \text{OCs} \times \text{hemisphere}}=0.77$
Nicodemus et al 2008	116 SZ spectrum disorders, 134 HC	<i>AKT1, BDNF, CAPON, CHRNA7, COMT, DTNBP1, GAD1, GRM3, NOTCH4, NRG1, PRODH, RGS4, TNF-alpha</i>	Obstetric Complications (OCs)	SZ	Interactions between serious OCs and: - <i>AKT1</i> rs1130233. - <i>BDNF</i> rs2049046 and rs76882600. - <i>DTNBP1</i> rs875462 - <i>GRM3</i> rs7808623 - No GxE interaction in controls.	p=0.031; OR=3.97 p=0.019/0.015; OR=12.45 p=0.031; OR=9.49 p=0.061; OR=3.39
Kéri et al 2009	200 SZ	<i>NRG1</i>	Psychosocial stress	Unusual thoughts	-Two-way interaction between genotype and family interaction type. - <i>T/T</i> genotype associated with unusual thoughts during conflict-related interactions. -No association during neutral interactions.	p<0.0001; F(2,197)=17.98 p<0.0001 p=0.5

Author	Sample size	Candidate G	Candidate E	Outcome Variable	Results	Statistics
Simons et al 2009	579 young adult female twins (general population)	<i>COMT</i> Val(158)Met <i>BDNF</i> Val(66)Met	Stress (ESM)	Feelings of paranoia in daily life (ESM)	- <i>COMT</i> :Val/Val x "event stress" x paranoia interaction. No interaction with "social stress". - <i>BDNF</i> : Val/Met x "event stress" x paranoia interaction. No interaction with "social stress"	p=0.002; β =0.05 p=0.10; β =0.02 p<0.001; β =0.04 p=0.33; β =0.05
vanWinkel et al 2008	31 psychotic disorder + cannabis, 25 HC + cannabis	<i>COMT</i> Val(158)Met	Stress (ESM)	Psychotic experiences (ESM)	-Significant Met/Met x ESM stress x psychotic experiences interaction -Similar results for ESM delusions. -No interaction in controls.	p=<0.001; β =0.77 p=0.01; χ^2 =12.4 p=0.20; χ^2 =3.3

Table 3. *AKT1* = Serine-threonine protein kinase; *BDNF* = Brain-derived neurotrophic factor; *CB1* = Cannabinoid receptor type 1; *CAPON* = Carboxyl-terminal PDZ ligand of neuronal nitric oxide; *CHRNA7* = Neuronal acetylcholine receptor subunit alpha-7; *COMT* = Catechol-O-methyltransferase; *DTNBP1* = dystrobrevin-binding protein 1; ESM = Experience Sampling Method. *GAD1* = Glutamate decarboxylase 1; *GRM3* = Metabotropic glutamate receptor 3; HC = Healthy Controls; *HLA* = Human Leukocyte Antigen; *MTHFR* = Methylenetetrahydrofolatereductase; *NOTCH4* = Neurogenic locus notch homolog protein 4; *NOS1AP* = Carboxyl-terminal PDZ ligand of neuronal nitric oxide synthase protein; *NRG1* = Neuregulin; *PRODH* = Prolinedehydrogenase; *RGS4* = Regulator of G protein signaling 4; SZ = Patients with Schizophrenia; *TNF-alpha* = Tumor necrosis factor.

The particulate nature of the molecular element to GxE interaction means that genetically pre-ordained outcomes could in theory be averted. The extent to which this is true depends on the effect sizes involved and whether the proposed intervention can be made in timely fashion. This has positive implications for public health. For example in some circumstances, it may be preferable to eliminate the environmental risk component altogether, rather than attempt the more tedious task of targeting genetic risk groups for a given intervention. Phenotype expression is normally suppressed as risk-inducing environmental exposures become scarce; this correlates with a decline in heritability and impacts on the number of diagnosed cases. The contextual nature of heritability can be exploited through use of the 'exposure only' study design⁸⁷, which facilitates the detection of environmentally-sensitive genetic variation. This approach is particularly powerful at the genome-wide level. The success of such strategies is determined by the extent of GxE contribution to the heritability of a given disorder.

A good illustration of the relationship between exposure and heritability comes from a US study that compared interstate influences on the heritability of teenage nicotine use. It was found that heavier state control of tobacco availability, through a combination of higher taxation, lower advertising and controlled vending machine supply, resulted in lower levels of detectable genetic influence on daily smoking⁸⁸. The high incidence of Schizophrenia could benefit from interventions in several areas of public policy. First and foremost would be those policies that made it more difficult to acquire cannabis, as this could reduce rates of Schizophrenia within genetically-prone sub-populations.

6. Methodological constraints in GxE research

There are lingering doubts about the experimental validity of many GxE findings reported in the literature. This is in contrast to the renewed sense of optimism about genetic association, a method which focuses on direct gene effects rather than the consequences of their interactions. Genetic association studies now have GWAS to look to as a methodological reference point^{4,38,40,41,50,56,89}, and it is out of the technological infrastructure supporting GWAS, that two competing theories (they may not be mutually exclusive) regarding the genetic architecture of Schizophrenia have emerged: The Common Disease-Common Variant and Multiple Rare Variant hypotheses^{4,9,10,58}. The latter of these will be explored in great detail through new sequencing initiatives already underway for Schizophrenia (for example, the UK10K study: www.uk10k.org/goals.html).

A combination of meticulous study design, unprecedented sample sizes and good governance over methodological practice⁹⁰, now mean that replication is no longer the rarity it once was for genetic association studies (see table 3). This is in part due to the fact that genetic association studies are becoming more methodologically homogeneous; many of the rigorous methodological practices and standards routinely implemented in GWAS research (internally validated findings, population stratification, etc) have also been widely adopted by studies whose scope does not extend beyond individual candidate genes.

In contrast, the diversity of methodologies and standards used in GxE research has remained stubbornly heterogeneous to date; the multitude of study designs used to follow-up new discoveries, has seen only varying levels of success⁹¹. Longitudinal studies sit very high within the complex methodological hierarchy of epidemiological designs, but even they are failing to provide the swift resolutions hoped for, to ongoing research questions of high importance (eg. Caspi vs Zammit)^{92,93}.

Several recurring factors limit the success rate of replication attempts in GxE research. These include:

- Measurement error
- The distribution of genotypes and exposure
- The effect size
- Sample size

The next section is dedicated to exploring each of these aspects in greater detail.

6.1 Measurement error

Arguably the most replicated GxE finding in Psychiatry belongs to the field of Depression, and involves the short allele of the Serotonin transporter gene (*5HTTLPR*) and Stressful Life Events (SLE), which interactively augment the risk of Depression⁹⁴. Reviews that have delved into the matter of how consistently the finding can be reproduced, have noted that there is an inverse relationship between sample sizes and the associated likelihood of replication. This appears to be due to the larger degree of measurement error (associated with exposure) inherent to large studies⁹⁵. Small studies, which have fewer resources, shun large-scale recruitment, but place greater importance instead on maximising the accuracy with which environmental exposures are measured.

Studies in which the SLE represents a single specific source of adversity, tend to extend the interaction trend, (even if they do not strictly reach the criteria of a 'replication' study) ⁹¹. This reaffirms the statistical importance of maintaining measurement error at low levels ^{96,97}. Opportunistic replication studies, typically performed using cohorts not primarily intended to address the original research question, tend to be more detrimental to replication efforts, as even variables with the same name can reflect either subtly, or grossly different constructs.

6.2 The distribution of genotypes and exposure

The issue of replication is further complicated by the fact that, depending on the frequency of the exposure, the same GxE construct may range from having:

- i. no effect when the exposure is low,
- ii. statistical interaction when the exposure is moderate, or
- iii. a main effect when the exposure is high ⁹¹.

As genotypic frequency has a similar influence on interaction detection, it is only recommendable to attempt the reproduction of an interaction in samples where exposure and allelic frequencies compare with the original study. Additionally, power to detect interactions is optimal only when both minor allele frequencies and exposure rates are at the 50% level. Idealised distributions such as these are unlikely to occur under normal recruitment conditions, although they can be ensured by the use of selective sampling ⁹⁸. Deviation away from these two statistical optima may, along with other methodological deficiencies, compromise the overall power of a GxE study.

6.3 Effect sizes

Biological interactions need not give any statistical clues to their existence. This is demonstrated by the example of Phenylketonuria (PKU), (a syndrome that gives rise to neurodevelopmental and psychiatric symptomatology). PKU results from a combination of allelic deficiency in the gene encoding the phenylalanine hydroxylase enzyme, and dietary exposure to phenylalanine. In this case, any statistical trace of this biological interaction is obfuscated by the ubiquitous nature of phenylalanine in the human diet.

A typical GxE analysis requires large samples to facilitate the detection of targeted effects. A wider debate surrounds how these interactions should be scaled. In order to determine the presence of an interaction, a product term is added to the regression model. In linear regression, the regression coefficient of the product term defines interaction as departure from additivity, whereas an interaction using logistic regression indicates a departure from multiplicativity ⁹⁹. An additive model is thought to best approximate the concept of biological interaction ¹⁰⁰, though this view is heavily contentious. Meanwhile multiplicative effects, though more difficult to interpret, generally allude to larger effects on risk, and so are still predictively useful.

Biological validity remains a panacea for all GxE research, as the concept of a purely biological interaction is easy to understand and design interventions around (assuming the consequences of the interaction is large enough to merit this course of action). In contrast, inferring a mechanistic relationship out of a statistical effect, relies on conditions and

assumptions¹⁰¹ that may not necessarily hold true for Schizophrenia⁸⁵. A statistical interaction may still have great predictive value nonetheless.

The difference between these two definitions (of Biological versus Statistical Interaction) can be problematic, as there remains plenty of scope for conflict between the two. In some cases discrepancies between the two may be artefactual. For example, the logarithmic transformation inherent to the multiplicative model can cause *bona fide* interactions to disappear, or else induce them spuriously⁸⁶, (an important caveat of this strategy).

These issues have fuelled a debate about the more appropriate way to scale interaction effects eg.^{85,86}. Some of the rhetoric surrounding this issue is seemingly prejudicial to the question of whether GxE research can make a positive contribution towards Schizophrenia's translational goals⁸⁵. A key step to obtaining a definitive answer to this question will be the introduction of more systematic approaches to GxE discovery. The model for the type of approach needed is epitomised by GWAS^{102,103}. In the future this will be further complemented by the genome sequencing projects now underway in Schizophrenia¹⁰⁴ (also see details of the UK MRC's cross-disorder sequencing initiative, the UK10K study; <http://www.uk10k.org/>).

6.4 Sample size

The tendency to overstate initial effect sizes results in a phenomenon known as 'winners' curse'¹⁰⁵.

Sample sizes in a replication study must accordingly be adjusted (upwards) to compensate for this associated loss of power. This is a practice embraced by the genetic association field of late, due to a combination of good governance⁹⁰ and a 'trickle down' of good research etiquette from GWAS, through to mainstream (candidate gene) genetic research.

A similar level of rigour is lacking from GxE research. This is worrying on two counts. Firstly, because from the outset, the power of an interaction analysis is typically lower than it is for a study of main effects¹⁰⁶, and secondly, the GxE field has tended to avoid facing such issues head on. This is typified by a reluctance among researchers to divulge vital information regarding statistical power in many instances⁸⁴. Such *faux pas* are propagated by the willingness of reviewers to accept such work, without enforcing appropriate disclosure of this information.

7. 10 years of GxE research in psychiatry – A post-assessment review

A recent critical appraisal shines a spotlight on the immediate shortcomings of GxE research in the psychiatric field⁸⁴. Its findings are still being digested by the psychiatric research community¹⁰⁷. A main accusation again centres on underpowering, (described by its authors to have skewed a decade's worth of research). Face value interpretation of their calculations suggests that average effect sizes would have to be 10 times larger than those normally found in GWAS, for the small sample sizes used to be even remotely credible⁸⁴.

The problem of underpowering was found to have a bi-directional relationship with publication bias, (the tendency to only report trends that support a given hypothesis). The

authors' report outlines an interesting chain of events, initiated by the instinctive preference among journal editors for novel findings. This distortion of the literature is sustained by additional biases that favour the publication of corroborating evidence, at which point statistical considerations such as power and study design are less rigorously enforced⁸⁴. Leniency in areas such as sample size and study design has long been self-evident in GxE research^{91,95} but can, for the first time, be quantified; studies which have failed to replicate an existing discovery are, on average, 6 times larger than studies that did manage to replicate. This suggests that the sample-size threshold required for a negative finding to be published is 6x higher than that of a positive study⁸⁴.

One non-intuitive factor that such appraisals have failed to acknowledge is that samples characterised by a low n may also be those most immune from measurement error⁹¹. For the 5HTTLPR x SLE interaction alone, low measurement error has been qualitatively shown to be the single most important determinant of a successful replication^{91,95}. Simulations of measurement error by Wong et al help to qualify this point⁹⁶. They suggest that an increase in correlation with true values of 'E' from .4 to .7 can equate to as much as a 20-fold gain in sample size. It is apparent therefore, that any review of the field must take into account the fact that the problem of a small sample can, to an extent, be overcome by maximising the precision of environmental measures. These days purposefully-designed tools (eg. <http://www.hsph.harvard.edu/faculty/peter-kraft/software/> or the ESPRESSO power calculator at <http://www.p3gobservatory.org/powercalculator.htm>) allow one to factor-in the variable precision of exposure measurement to estimations of power.

But in its defence, the Duncan-Keller assessment (a systematic assessment of 103 studies over a 10-year period) extends way beyond the Serotonin transporter. Therefore the critique is a formulation which applies to the field as a whole. Its take home message suggests that replication studies in Psychiatry currently only rarely achieve what they purport to, to a satisfactory standard.

This message is resounding, and also provides a convenient narrative for the poor progress made in bringing new findings to the clinic. At present it is largely explained by the shortage of high quality evidence entering the translational pipeline.

The crystallisation of lessons learned over the past 10 years⁸⁴ should be capitalised upon to make this a watershed moment for the application of GxE methodology in Psychiatry. However the type of cultural revolution needed can only be prompted by:

- i. An all-encompassing redefinition of what constitutes methodological good practice in GxE research¹⁰⁷ (this could be achieved by developing something equivalent to the STREGA (*ST*rengthening the *RE*porting of Genetic Associations) principles, specifically for the GxE research.
- ii. A consensus between journal editors, reviewers and researchers that these guidelines should be adhered to.

8. New horizons in GxE research

8.1 GxEWAS: The systematically tractable meets the biologically plausible

The archetypal approach to identifying potential GxE candidates avoids the statistical pitfalls of multiple testing, and is instead guided towards appropriate candidate regions

through a combination of biological theory and functional evidence ⁸². Given our rudimentary understanding of the complexity encoded at the genomic level, it is perhaps not so surprising that the doctrine of 'biological plausibility' is often questioned. Additional scepticism is reserved for the notion that the molecular dissection of psychiatric phenotypes can be formularised ⁸². This is a pertinent point, given that GWAS has shown us that the underlying biological basis of many complex and Mendelian traits is largely abstract in nature.

Advocates of the biological plausibility doctrine can rightly point to the robust experimental and analytical settings in which several of these discoveries have been made ^{93,94,108}. However detractors often cite the peculiarly low level of GWAS support for traditional Schizophrenia candidate gene favourites, (all of which are 'plausible' in one way or another), ^{109,110} to suggest the perils of a religious fixation on biological dogma ⁸⁴.

The apparent discord between candidate-gene and GWAS findings is typical for most of Psychiatry, with very few exceptions ¹¹¹ (convergent GWAS and candidate-gene findings in Schizophrenia are noted in table 2). If anything, GWAS has diverted attention towards less-obvious genomic points of interest, many of which lie within the non-coding domain.

Thus the non-coding genome has proved to be a rich source of pathogenic variation; approximately 90% of all GWAS findings (across disorders) originate from there. But for now, the jury is still out regarding the possible contribution of first-generation candidate genes to the risk, pathology and outcome of Schizophrenia. The delay in implementing GxE studies of Schizophrenia means that the relevance of historical genetic candidates to the GxE paradigm remains untested in modern-day genome-wide protocols. It is still premature therefore, to exclude a possible wider role for some of these genes in the aetiological or pathological course of Schizophrenia.

GxE studies are steadily becoming entrenched in the literature. A number of neuro-developmental and neurological phenotypes have already been investigated. These highlight interactions ranging from the effect of coffee-drinking on Parkinson's Disease, to the effect of adverse intrauterine environments on brain growth ¹¹²⁻¹¹⁴. As this innovative branch of genomics is yet to take off in Schizophrenia, the current crop of GxE findings both in table 3 and in other areas of Psychiatry, are still yet to face the same acid test used to put the previous generation of association candidates on trial ^{109,110}. GxE is currently one of many longer-term aspirations for policymakers in the Psychiatric Genetics community ¹¹⁵.

Several alternatives to standard Case-Control analysis methods will be at the disposal of the community by the time this occurs. Bayesian Case-control approaches already feature among them ¹¹⁶. However the Case-only model is currently considered to be the most effective (in terms of power and efficiency) methodology for this branch of research ^{117,118}. The one proviso of the approach is that genes and exposure must be independent in the population from which cases are drawn ^{117,119}. This condition can be tested directly, by repeating the GxE analytical procedure on controls, and appropriately filtering out signals (that cross the designated threshold of significance) from the case-only study.

Post-genomic technological advances, namely the advent of micro-array technology, have led to huge increases in the scale at which genetic variation can be sampled from a genome by a single study. The abundance of this data can propel the formulation of *post-hoc* hypotheses based on biological plausibility. Useful resources that can help to inform the decision-making process include tools such as the UCSC and ENSEMBL genome browsers (<http://genome.ucsc.edu/cgi-bin/hgGateway> and <http://www.ensembl.org/index.html>). These contain a wealth of information highlighting the organisation, structure and function of the genome. Other specialist resources provide a dense functional annotation of regions that border GWAS hits (<http://jjwanglab.org:8080/gwasdb/>)¹²⁰.

One area in which Schizophrenia genetic research has been slow (compared to other fields such as Alzheimer's Disease), is its readiness to combine genetics with other flavours of system biology that can now be feasibly explored. This multi-level approach could provide insights about fundamental bio-mechanic processes that lie at the heart of gene-environment interaction.

One potential class of mediaries are known as Quantitative Trait Loci (QTLs). These are regulatory variants associated with control of gene-expression (eQTLs), protein levels (pQTLs) and gene activation status (methQTLs).

The ever-decreasing cost of implementing these system-based biological approaches continues to increase their accessibility. Meanwhile, whole-genome sequencing provides the means to increase both the resolution of regulatory variants across the genome, and the fuel for further biological hypotheses.

A key objective within the universal objectives of personalised medicine (to which the field of Psychiatric Genetics is also subscribed) is to enhance both the visibility and efficiency with which promising new evidence is vetted and then turned into new diagnostics and treatments. Crucially however, neither a purely biological, nor a purely systematic approach, (such as GxEWAS) can secure these goals alone. This is due to two main reasons:

- Exhausting the investigation of all plausible biological hypotheses using available genomic and enviromic data, is a slow, painstaking process that is difficult to fully automate. In any case we lack the fundamental insight about underlying biological mechanisms to assume we can become routinely successful at this.
- Meanwhile systematic methods such as GxEWAS may be too cursory. They must in any case, first confront the reasons why smaller candidate-based studies of GxE so regularly out-perform larger ones, lest the same mistakes of candidate GxE research simply end up being repeated, on a yet grander scale⁹¹.

The many lines of derivative research resulting from GWAS in Schizophrenia collectively demonstrate how both systematic and biological candidate approaches can work in tandem^{55,103,115,121,122}. Thus, an emphasis on *post-hoc* explorations of candidate pathways, genes and variants may be the best bet for turning a cursory screen of the genome (such as GxEWAS) into something that is potentially much more substantive. This kind of combinatorial approach, which marries systematic and hypothesis-led discovery through data-mining, may one day reveal (and explain) the true pervasiveness of GxE in Schizophrenia.

8.2 Strategies for data harmonisation and how this will help

Observations by Caspi ⁹¹, Uher and McGuffin ⁹⁵, Vineis ⁹⁷ and Wong ⁹⁶ collectively highlight the challenge of balancing sample size and measurement error for optimal statistical benefit. It is in this respect that the Dunedin study (to which a disproportionate number of GxE discoveries belong) enjoys an unparalleled advantage over many of the cohorts that have since revisited the original *5HTTLPR* finding. The study combines the higher accuracy of exposure measurement often found in smaller studies, with a large sample size that is so often elusive.

A large number of replication studies do not share this same rare-but-optimal combination of properties ^{91,96,97}. It is this variability which may be incapacitating to the field as a whole.

Such problems can be addressed by applying greater epidemiological rigour to the collection, storage and power of genetic datasets. The rapid proliferation of biobanks in biomedical research is accompanied by the expectation that this will directly improve the quality of translational research, (and not just for Schizophrenia). Biobanks provide a means to satisfy the growing demand for high quality population data, thus they will be a key driver of genetic discovery in the future. They will also be an essential resource for validating discoveries made elsewhere.

Of course genetics is just one of many important biological areas that can be served by such resources. This is why the rapid proliferation of biobanks is vital, even for the many non-psychiatric traits that have, to a large degree, already profited from GWAS. This includes traits such as Age-related Macular Degeneration, Prostate Cancer, Coronary Heart disease and type 2 Diabetes ⁶⁵.

The primary functions of a biobank include:

- Processing and storage of biological samples.
- Collection of phenotype and other data
- Facilitating statistical analysis.

A recurrent concern among commentators in the GxE field is the increased scope for measurement error in these heterogeneously-assembled datasets ⁹¹. Additional problems may occur due to the fact that geneticists, epidemiologists, biologists and biostatisticians, often use different vocabularies ¹²³. Extrapolating these issues to the large number of biobanks in existence around the globe suggests that there is a need for overall governance to maximise data harmonisation. A large number of international bodies have been created for this purpose, many with overlapping functions. For example in Europe, PHOEBE (Promoting Harmonisation Of Epidemiological Biobanks in Europe), ENGAGE (European Network of Genomic and Genetic Epidemiology) P3G (Public Population Project in Genomics), are three independent organisations that provide a continent-wide consensus on procedures ranging from collection, storage and format of biological samples and associated data.

Perhaps this overlap is needed to counteract the organisational absence of other major institutions from this exercise. Regulatory bodies such as the European Medicines Agency (EMA) and The Food and Drug Administration (FDA) were at some point considered, but ultimately deemed too inherently conservative to oversee such a task ¹²⁴. Top-down

implementation of new and emerging international standards and protocols for data collection, sample acquisition, etc is managed by national biobanking initiatives, such as the UK Biobank. Policies may then be channelled down to a set of regional hubs such as the National Institute for Health Research's Biomedical Research Centres (UK). It is encouraging that Schizophrenia research is now beginning to derive the benefits of biobank-based research ¹²⁵⁻¹²⁷.

8.3 A note on methods for research synthesis

Such initiatives inevitably generate an abundance of data. A critical mass of high quality data is usually the trigger for the synthesis of this evidence to begin. This typically uses meta-analysis, whose conventional format uses the null hypothesis (a construct of frequentist statistical theory) as its reference point. However the rationale for this becomes increasingly questionable as new evidence is added to an existing literature ^{128,129}. A Bayesian approach (ie. one that would allow the posterior probability of a hypothesis to be derived from prior knowledge, after taking into account new data), would allow any uncertainty about a hypothesis, to be acknowledged in an adaptive way.

The conspicuous absence of Bayesian methods from the science of data synthesis was only recently lamented, by key stakeholders involved in the process of evaluating new drugs for the UK's National Health Service ¹²⁸. Such messages may yet help to expedite the uptake of these methods, although there is already evidence of their adoption in clinical trial research ¹²⁸. These methods could widen the net used to gather new evidence, by allowing the incorporation of data from *in vivo* and cellular studies into the evaluation process. Thus Bayesian methodologies could provide an important means of channelling a wide range of functional evidence into synthesised data ¹³⁰, as well as providing an alternative set of rules for assessing the validity of a hypothesis.

8.4 The future of clinical databases in psychiatric GxE research

It will soon be much easier to harvest the valuable clinical data derived out of even routine patient contact with clinical services, given that a switch-over to electronic medical records (EMRs) is now underway. The integrative blueprint for the new digital clinical age would allow a comprehensive (clinical, molecular and environmental risk profile) to be compiled for each patient. The front-end portal for this is as a personal record that follows the individual around as they move between different mental health institutions. Back-end access to such data is possible (for research purposes), but necessarily anonymised. The information itself can be processed in a way that allows even the interrogation of unstructured data (eg. clinical notes) to now be formularised (eg. see ¹³¹). The huge potential of EMRs represents great scope for integrative research. It is anticipated that such resources will:

- Continue to drive understanding of molecular aetiology, by harnessing patients for *in silico* (bioinformatically-oriented) studies.
- Allow more efficient stratification of patients for interventions or clinical trials
- Improve the quality of genetic counselling, which will be based on a fuller, all-encompassing profile on which to base evaluations of risk, treatment outcomes and prognoses.

The true potential of the EMR model will become more apparent only when high-dimensional genetic and molecular profiling becomes economically feasible and clinically routine. This will make it practically possible to integrate a whole manner of clinical data into diagnostic/prognostic genetic research. But such times are almost already upon us, thus we do not have far to search, to find examples of how an integrative approach may work in practice. One such model is that of Ashley and colleagues¹³², who recently reported a far-reaching genomic health assessment of a patient showing a strong familial indication of Coronary Heart Disease and Sudden Death Syndrome. A graphical account of the relative genetic liability for other disorders (Coronary Artery Disease, Obesity, Osteoarthritis and Type 2 Diabetes) depicts the genetic relationship between these disorders and several conditional environmental risk exposures, (stress, smoking, exercise and diet).

For Schizophrenia, a more precise account of the relationship with environmental risk factors could be achieved with the help of a new generation of instruments (questionnaires) and devices that will enable their measurement to be conducted with greater sensitivity than ever. Many examples of these have been devised for a large multi-centre study: The European network study of Gene-Environment Interaction (EUGEI)⁵. Of particular relevance is a work package entitled 'Functional Enviromics', which aims to take the elucidation of socio-environmental risk factors for Schizophrenia to a level of resolution not previously reached.

9. New horizons in pharmacogenomic research

9.1 Background

One consequence of GxE interaction is that any undesired outcomes can be averted through interventions targeted at the level of the individual, or the population, through changes in wider socio-economic policy. Primary avenues of social intervention for Schizophrenia would include redressing social inequalities², as well as challenging permissive attitudes to the use of illegal psychotogenic substances which, in tandem with other risk factors, help to sustain the high level of psychosis in the general population.

Meanwhile, molecular strategies for moderating or ameliorating the detrimental consequences of GxE interaction, fall within an area of personalised medicine known as Pharmacogenomics. This discipline is concerned with devising optimal therapeutic treatments for genetic sub-groups of patients. A competing goal is to minimise the risk of ill effects resulting from such treatments. Large inter-individual variability in both drug response and side-effects are the main foundation for this branch of research¹³³. Much of this variability can be traced to genetic variation within key liver enzymes (the cytochrome P450 complex). It is the fate of all antipsychotic drugs to be channelled to this biological complex for breakdown (see table 4).

Of all the enzymes known to have a role in the metabolism of antipsychotic drugs, *CYP2D6* has been the most extensively characterised. This is not a great surprise, given that the protein product of this gene catalyses the breakdown of up to 25% of all pharmacological compounds. Current knowledge about functional variation within this gene alone is enough

to explain inter-individual differences in drug efficacy. For example, 2% of Caucasians and 25% of East Africans who express multiple functional CYP2D6 alleles, (ultra-rapid metabolisers) can be phenotypically distinguished on account of having the poorest levels of response to specific treatments^{134,135}. Unfortunately however, current assessments of the clinical utility of pharmacogenetic testing in Schizophrenia, suggest that a heavy reliance on CYP2D6 genotyping is currently not the most beneficial way to formulate prescribing guidelines regarding the use of antipsychotic drugs¹³⁴. A similar study of CYP2D6 (looking at Selective Serotonin Re-uptake Inhibitor treatments in Depression), recently came to a similar conclusion¹³⁶.

Table 4. Commonly used antipsychotics metabolised by CYP enzymes

Enzyme	Typical Antipsychotics	Atypical Antipsychotics
CYP2D6	Primary metabolism Chlorpromazine Haloperidol Perphenazine Thioridazine	Primary metabolism Risperidone
	Secondary Metabolism Zuclopenthixol	Secondary Metabolism Olanzapine Quetiapine
CYP1A2	Primary metabolism Chlorpromazine Perphenazine Thioridazine	Primary metabolism Clozapine Olanzapine
	Secondary Metabolism Haloperidol Perphenazine	
CYP3A4	Primary metabolism Haloperidol	Primary metabolism Quetiapine Ziprasidone
		Secondary Metabolism Clozapine Olanzapine Risperidone

Table 4. (Adapted from reference¹³⁴)

9.2 A generalisable translation framework for GxE discovery

Poor performance of novel findings across different formulations of synthesised data represents an obvious barrier to clinical translation. But even if this obstacle can be overcome, a further series of hurdles may replace it. A clear framework now exists to prompt and signpost the long path between discovery and clinical application¹³⁷. Implementation of the framework is marshalled by the Human Genome Epidemiology Network (HUGENET), a global collaboration of individuals and organisations whose remit is to assess the impact of genomic variation on population health. According to HUGENET, the pathway to clinical translation can be divided into four key stages (see table 5).

Table 5. The 4 phases of clinical translation

Translation Research Phase	Example	Study Approach to overcoming phase
Phase 1: Discovery and Clinical validity	eg. Reliable series of associations between a SNP and drug response	Phases I and II clinical trials; observational studies
Phase 2: Clinical Utility to Clinical guidelines	Does SNP improve drug response and what is its predictive accuracy?	Phase III clinical trials; observational studies; evidence synthesis and guidelines development
Phase 3: Implementation in Clinical practice	Explore data regarding the uptake of the SNP test in clinical settings - explore potential barriers	Dissemination and implementation research; Phase IV clinical trials
Phase 4: Public Health Impact	Does SNP improve clinical outcome in the population?	Outcomes research; Population monitoring; Phase IV clinical trials

Table 5. Table 4 shows the 4 phases of clinical translation and the critical approaches required to negotiate each one. Though initially designed to provide a translational model for pharmacogenetic research, it can also be applied in the context of GxE research. (Adapted from references ^{138,139})

Although this framework has been developed to support emerging new pharmacogenomic technologies, devices and treatments, its generic nature means it provides a model that is also extrapolable across genetic research (including GxE). The model adopts the ACCE (Analytical validity, Clinical Validity, Clinical Utility) and ELSI (Ethical, legal, social issues) criteria to ensure a rigorously vetted transition between phases ¹³⁹. The solid foundation provided by the framework will help to ensure that promising findings do not become ‘lost in translation’ ¹⁴⁰, a problem that has characterised the last 60 years of drug development. This issue still continues to affect the industry acutely: It takes an average of 17 years for just 14% of new scientific discoveries to enter day-to-day clinical practice ¹³⁷, while the cost per successful drug exceeds \$1billion, after adjusting for all the failures ¹⁴¹.

9.3 Regulation and decision-making

Regulatory governance fulfils several objectives, the most important of which is to ensure that patients and research subjects are protected from any undesired consequences (‘adverse events’) of new drugs intended for the market. GxE discoveries that make it into clinical evaluation phases fall under the jurisdiction of various geographical regulatory institutions such as the European Medicines Agency (EMA) in Europe, the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK, and the Food and Drug Administration (FDA) in the US.

Adherence to the process of regulation is essential for ensuring a smooth progression through the translation scheme outlined in table 5. For instance, failing to procure accreditation for genetic tests and therapies from decision-making bodies such as the EMA and the FDA tends to adversely affect the uptake of these innovations in other global regions. This may partly explain the poor uptake of CYP2D6 and CYP2C19 genetic tests observed in a recent Danish study ¹⁴².

However, over-zealous regulation can itself create obstacles, particularly if perceived to be of no discernible benefit to patients ¹⁴³. This has potentially been the case in Europe, where the much-criticised 2001 European Union Clinical Trial Directive has caused the cost of

running clinical trials to spiral. Other knock-on effects attributed to the legislation include a 30% decline in the numbers of participants agreeing to take part in trials across Europe, over the last few years ¹⁴⁴. As clinical trials are an integral component within any translation scheme, such problems threaten to create a fatal bottle-neck in the pipeline, for discoveries that might otherwise have made it through the process relatively unscathed.

An overhaul of regulatory governance at national level has been proposed to circumvent this problem. In the UK, it is being done in conjunction with The National Institute for Health and Clinical Excellence (NICE), an organisation primarily responsible for assessing the cost-effectiveness, on behalf of the National Health Service (NHS), of providing new therapies and treatments. However the change of UK government means it is not even clear that there is a timetable for putting such proposals into practice ¹⁴³.

As just hinted at, all novel genetic discoveries (including GxE interactions) that have safely negotiated the rigours of the validation stages shown in table 5, must still run the gauntlet of proving their overall cost-effectiveness, before they can progress beyond validity, into utility. But new technology and treatments can only be considered to be cost-effective if their health benefits can be shown to outweigh the opportunity costs of services or treatments that they may displace ¹⁴⁵. When viewed in the context of the many benefits that personalised health care will bring, the additional expenses inherent to many new genomic technologies, are unlikely to present much of a barrier to widespread uptake.

10. Conclusion

Lessons of the past decade of GxE research in psychiatry (and more specifically, Schizophrenia) mean that the focus of the next should be to ensure that effort and resources already spent, or else earmarked for future investment, do not go wasted. In order to ensure this a course of greater methodological rigour should be pursued.

It would be advantageous to complement this with the encouraging array of new specialist tools, methodologies and infrastructures available, some of which are highlighted in this article. A combination of falling economic costs and increasing accessibility make this proposition the most practical and logical way forward. In the category of 'methodologies' we additionally include innovations that enable the epigenomes, transcriptomes and proteomes of Schizophrenic patients to be characterised in high-dimension. Each of these domains reflects a different dynamic (and environmentally-responsive) element within a broader biological scheme. But each also remains curiously under-represented in mainstream GxE research today. This is despite evidence to suggest they may serve a functional purpose as biomarkers of environmentally-induced pathogenesis, susceptibility, illness progression and treatment outcome ¹⁴⁶⁻¹⁵². Despite these documented examples, each discipline also faces thematic questions about how to achieve methodological best practice, given their various respective constraints ^{147,153,154}.

Thus the current outlook would suggest that no single biological domain will have a monopoly on the clinical insights that may yet emerge out of future studies that may link genes, environment and Schizophrenia. The option to harness the various biological domains collectively, with genetics as the focal point, is promising, but currently under-resourced ¹⁵⁵⁻¹⁵⁷. But this type of expansive approach is additionally attractive and may propel us towards fulfilling the unrealised clinical ambitions of GxE research.

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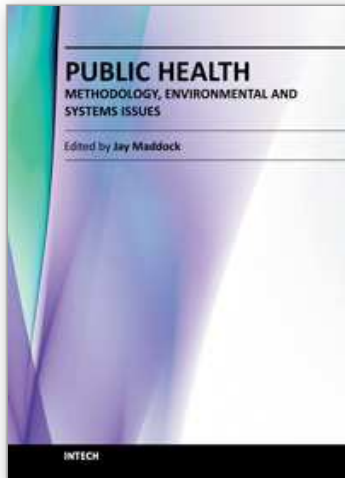
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