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Article

Nick Martin's Contribution to GxE Research

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Abstract

The study and identification of genotype–environment interactions (GxE) has been a hot topic in the field of human genetics for several decades. Yet the extent to which GxE contributes to human behavior variability, and its mechanisms, remains largely unknown. Nick Martin has contributed important advances to the field of GxE for human behavior, which include methodological developments, novel analyses and reviews. Here, we will first review Nick's contributions to the GxE research, which started during his PhD and consistently appears in many of his over 1000 publications. Then, we recount a project that led to an article testing the diathesis-stress model for the origins of depression. In this publication, we observed the presence of an interaction between polygenic risk scores for depression (the risk in our 'genotype') and stressful life events (the experiences from our 'environment'), which provided the first empirical support of this model.

Keywords: depression; Gene–environment interaction; GxE; human behavior; Nick Martin

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Nick Martin's interest in genotype–environment interactions (GxE) and genotype–environment correlation (covGE) can be traced back to his PhD thesis in Birmingham (Martin, 1976). Part of his PhD work on the topic was published in the 1977 paper, 'A Progressive Approach to Non-Additivity and Genotype-Environmental Covariance in the Analysis of Human Differences' (Eaves et al., 1977), co-authored with Lindon J. Eaves (Nick's PhD advisor), Krystyna A. Last and John L. Jinks (Lindon's PhD advisor and precursor on the topic; Jinks & Fulker, 1970). The article of 42 pages reviews the interpretation, estimation and statistical power of many difficult concepts (including GxE, covGE and assortative mating). Together with Boomsma and Martin (2002), we find the first statement of the abstract still accurate more than 40 years later, despite many publications in those topics.

> No aspect of human behaviour genetics has caused more confusion and generated more obscurantism than the analysis and interpretation of the various types of non-additivity and non-independence of gene and environmental action and genotype-environment interaction and covariation, dominance and assortative mating. (Eaves et al., 1977, p. 1)

In this article, Nick Martin is credited with empirically demonstrating during his PhD that interactions may be dependent on the choice of scale (Eaves et al., 1977; Martin, 1976). This is particularly important for psychometric scales (such as the personality and attitude factors used as examples) dependent on item selection, item weighting and scale transformation. Thus, scales must be chosen for their interpretability and that of the resulting statistics, keeping in mind there is not such a thing as a 'true' scale. In addition, even if a change of scale may represent a change of trait, sensitivity analyses may be used to evaluate the effect of scale distribution on the conclusions (Eaves et al., 1977).

In addition, Nick suggested the presence of GxE on behavioral traits (Martin, 1976) by studying monozygotic (MZ) twin-pairs raised together (Jinks & Fulker, 1970). This design relies on the fact that any GxE effect introduces a correlation between the MZ pair mean and the absolute intrapair variance. Thus, a correlation between absolute within-pair differences and mean value of an MZ pair suggests the presence of GxE, although it may also point toward an interaction between shared and unique environmental sources of variance (Jinks & Fulker, 1970). To note, estimating the GxE variance components (GxC and GxE) is limited by the fact it requires an extended twin design with twins reared together and apart, as well as unrelated individuals reared together (Eaves et al., 1977; Jinks & Fulker, 1970). However, unmodeled GxE can bias the heritability and environmental estimates from twin models (Eaves et al., 1977; Jinks & Fulker, 1970).

In 1987, Nick and colleagues performed simulations to estimate the statistical power of GxE analyses that used measured genetic loci and environmental risk factors (Martin et al., 1987). The authors considered an ascertained twin design, which estimated the main effects and the interaction of the measured genotype and environment and controlled for background genetic and environmental sources of variance. In addition, it allowed estimation of epistasis (interaction between measured loci and background genetics) as well as between measured environment and background genetics. This model was visionary, in that it prefigured controlling for background genetics (i.e., population structure) in association testing, while introducing genetic interaction analyses. Take it genomewide and you may recognize a modern linear mixed-model genomewide association study (GWAS; Yang et al., 2014) or a genomewide environment interaction study (Dunn et al., 2016). In addition, the article reports the important increase of

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statistical power arising from studying a continuous (i.e., cancer liability) over a discrete (i.e., cancer diagnosis) phenotype, which relates to the discussion on scale we mentioned previously.

A decade later, Heath et al. (1998) published the results of a twin model for a depression score, stratified by marital status, and concluded in favor of a modifying effect on the genetic liability for depression. In addition to his work on behavior, psychology, and psychiatry, Nick Martin also contributed to other areas of medical research, such as skin cancer — of special interest for Queensland, which still displays one of the highest prevalence in the world (Australian Institute of Health and Welfare and Australasian Association of Cancer Registries., n.d.; Staples et al., 2006). A GxE investigation in 2002 looked at the association between sun exposure and skin cancer, stratifying the analyses by familial risk (Siskind et al., 2002). The authors concluded there is an interaction between the familial risk (proxy for the cancer genetic liability) and sun exposure, albeit it was not directly tested.

It should come as no surprise that Nick was invited to contribute a book chapter about GxE concepts and methods (Boomsma & Martin, 2002), a very well written and documented introduction to GxE. Another review article focused on GxE in the context of alcohol use and twin models (Heath et al., 2002). It reiterates the power limitation of estimating the GxE variance components, or the need for twin designs that include twins reared apart. It also envisages that linkage analyses could pinpoint relevant loci, which would offer a direct measurement of genetic liability:

> Analyses of genotype x environment interaction effects will always be more powerful when genotypes as well as environments can be measured. In the alcohol field, the identification of polymorphisms that affect alcohol metabolism that are associated with differences in alcohol dependence risk offers rich, although as yet underexploited, opportunities for studying such effects. (Heath et al., 2002, p. 35)

When GWAS started to identify robust and replicated genetic loci — for example, the FTO variant associated with body mass index (Cornes et al., 2009) — Nick's GxE investigations resumed, this time focusing on individual genetic variants. The authors compared the intrapair variance of MZ twins for each FTO single-nucleotide polymorphism status and also tested the interaction between FTO and parity in women, none of which returned significant (Cornes et al., 2009).

It is worth mentioning another article co-authored by Nick Martin that described the genetic contributions shared between socioeconomic status (SES) and gambling (Slutske et al., 2015). By using the GxE twin model proposed by Purcell (2002), the authors showed a significant increase in genetic and environmental variance in gambling as a function of SES. In addition, the article reported that SES, often thought to be an environmental exposure, had a genetic component and showed a genetic correlation with gambling behavior (Slutske et al., 2015). In contrast, a similar analysis on the genetics of IQ failed to identify a significant interaction with SES (Bates et al., 2016).

We have focused on articles where Nick Martin is first or last author, but a quick search in his bibliography returns at least another 14 publications relating to GxE that he has contributed to.

In 2015, and more than 1000 papers after his PhD, Nick had a project to propose to us — to directly test the diathesis-stress model for the origins of depression. At this time, we were two very early career scientists (working in our PhD and first-year post-doc). We had just collaborated to calculate polygenic risk scores (PRS) on the participants of previous QIMR studies (Wray et al., 2007). At the time, psychiatric PRS were starting to show some level of prediction. We embraced Nick's project with enthusiasm: it meant a great opportunity to continue our work together, to learn and practice statistical skills, and to empirically test one of the main theories for the origins of depression. In our innocence, we did not foresee that the project would take us more than 2 years of hard work to complete. It was, however, totally worth the effort, and 'the diathesis-stress project' is to date one of our main scientific accomplishments (Colodro-Conde et al., 2017). Two similar initiatives were conducted at the time by other groups, which considered childhood trauma and stressful life events as environmental exposures (Musliner et al., 2015; Peyrot et al., 2014). Previous articles on the topic had used candidate gene approach, where the interaction was tested for with a single gene or a handful of loci (sometimes not robustly associated), leading to inconsistent results.

The diathesis-stress design benefited from the recent availability of predictive PRS, a direct measure of the diathesis (i.e., the genetic vulnerability/predisposition for a trait), in our case, depression. This made it possible to test for GxE using observed G and E (Heath et al., 2002). In practice, we tested the association between a depression score and the diathesis for depression (approximated by PRS, 'G'), stressful life events (stress score, 'E') and their interaction (GxE). In such a model, the GxE captures the multiplicative effect of genetic predisposition and environmental exposures on top of their additive contribution to the risk of depression. Data for the study were already available thanks to previous data collections (by Nick and colleagues; Gillespie et al., 1999; Kirk et al., 2000; Treloar et al., 1999).

The diathesis-stress study fits nicely in Nick's body of work. As previously flagged in Heath et al. (2002), this approach offered additional power compared to a variance component analysis where the G and/or E factors are not specified (Jinks & Fulker, 1970; Purcell, 2002). In addition, although limited to the genetic liability tagged by the GWAS summary statistics and the list of stressors collected, the GxE effect benefits from a greater interpretability (compared to global variance components), the sign of the interaction being one example (Eaves et al., 1977). Finally, this GxE investigation built on results from robust GWAS and methodological developments relative to genetic risk prediction, as anticipated in previous publications (Heath et al., 2002).

Our 'diathesis-stress' meetings took place every Tuesday. It was the three of us plus Gu Zhu, and Sarah Medland. Gu had worked with the stress and depression data and provided the item response theory (IRT) scores variables, while Sarah (who was Lucía's supervisor) contributed with her statistical expertise and critical thoughts along the whole project. Nick told us many times (and experience proved him right) that regular meetings are the only way to get a project moving. At one point, Nick reached out to other GxE experts to validate our approach and results. You can probably guess who he called: Andrew Heath and Lindon Eaves.

As we had undertaken this project in addition to our other workloads, we necessarily had to work some weekends. We usually met on Saturday morning at the markets, before eating together and working on the paper for the rest of the day, which sometimes extended to the Sunday (often with some party in between). Being a person who enjoys devoting his Sundays to work, reading and catching up with the literature, you could tell Nick was very proud of us and eager to hear every Monday about our studious weekend (as well as about the party). The truth is that we all enjoyed (with some doses of pain) every step of the process. This included clarifying concepts, the formulation of hypotheses, the computation of every variable and design of the analyses, as well as the huge

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amount of checks that we performed to convince ourselves the results were real. Nick took every opportunity to make us think and actively participate in all discussions — and so we did. We also appreciated his unlimited memory of the data collected at QIMR or the specific tables or figures in the papers that he wanted us to cite.

Nick arranged for us to have early access to the unpublished summary statistics of the GWAS meta-analysis run by the Psychiatric Genomics Consortium. We showed (Colodro-Conde et al., 2017) that the PRS computed with the updated GWAS offered a stronger measure of the diathesis for depression than the GWAS (PGC-MDD1; first GWAS of the Major Depressive Disorder (MDD) group of the Psychiatric Genomics Consortium (PGC) et al., 2013) used in previous publications (Musliner et al., 2015; Peyrot et al., 2014). More importantly, we found a significant positive interaction between the PRS for depression and the scores of (personal) stressful life events, accounting for social support and network life events, and controlling for the population structure (twin sample). This effect was replicated about a year later in the Generation Scotland dataset (Arnau-Soler et al., 2019).

However, the project did not finish there, and through a challenging revision process, we kept building on what Nick possibly enjoyed the most: the 'caveats' section. If some of you remember Nick presenting updates of the project at the time (e.g., Behavior Genetics Association meetings or the World Congress of Psychiatric Genetics between 2015 and 2017), you may remember that most of the presentation was dedicated to some of the issues discussed in the article. For those who missed it, the 'caveats' section included a sensitivity analysis of the effect of the measurement scale (IRT depression scale, raw depression sum score scale, as well as a DSM-IV (Diagnostic Statistical Manual, fourth edition) diagnosis in a logistic framework). Using the two depression scales, we found consistent interaction results, though the strength of the interaction varied greatly. Of note, the interaction did not reach significance (p = .059) when using the DSM diagnosis, though the sample size (hence power) was lower. The analyses stratified by sex did not return significance, although the statistical power was also lower. We also performed a Jinks and Fulker analysis on the MZ pairs (Jinks & Fulker, 1970), with results consistent with the presence of interaction (and scale effect). Further checks included investigating the source of the interaction by separating 'passive' from 'active' life events (Plomin et al., 1990), or by acknowledging that the stressful life events have a genetic component (Colodro-Conde et al., 2017; Kendler & Baker, 2007), which prevents from directly concluding the interaction is of the GxE type (vs. GxG). This important last point was raised by the reviewers and got solved that next Tuesday during our meeting (credit goes to Sarah Medland) — with Sarah, it took us less than 30 min to implement the analysis, which was all she had before her next meeting. The solution came from taking advantage of the twin sample, which was only a complication thus far, forcing us to use mixed models to account for the sample relatedness in the analyses. We fitted a multivariate twin model on the items of the stress score, which allowed partitioning the stressful life events score into a genetic and an environmental factor score. We confirmed that most of the observed interaction could be attributed to a GxE effect as opposed to a GxG effect (Colodro-Conde et al., 2017). To be exhaustive, there is one caveat we did not implement correctly, which related to controlling for all first-order interactions (Keller, 2014). This was pointed out by Matt Keller after the publication, and we went back to the data to make sure it did not change the results.

When the paper was accepted in *Molecular Psychiatry*, we all happily celebrated at Kafenio, one of Nick's favorite restaurants in Brisbane where beautiful characters serve delightful authentic Greek/Cypriot cuisine. The sense of accomplishment may have interacted with the buzzing effect of the wine, but we will seek replication to conclude about what caused the hangover.

Nick's energy and passion in research are contagious and have inspired us to work in research and human genetics in particular. We feel deeply grateful for having witnessed it from the front row, and possibly having fuelled it at times. This experience was extremely formative, and we both feel we have gained a lot more than a good publication. The epilog of the story could be a second project we embarked on almost immediately after, which focused on the genetic relationship between schizophrenia and population density of where people live (an idea of Marcella Rietschel; Colodro-Conde et al., 2018). It included a side GxE analysis of population density, with age as a modifier, which suggested genetic control over living environment increases with age. Nick did not find this result surprising, he had already published this result (Whitfield et al., 2005).

The overall contribution of GxE to most traits is still unknown yet heavily discussed. Evidence of specific GxE has been found for depression, but they individually do not explain a large fraction of the depression risk (Arnau-Soler et al., 2019; Colodro-Conde et al., 2017; Musliner et al., 2015; Peyrot et al., 2014). More research is needed, so what is your next idea Nick?

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