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Exploratory Workshop Scheme

Standing Committee for
The European Medical Research Councils (EMRC)
Life, Earth and Environmental Sciences (LESC)
Social Sciences (SCSS)

Scientific Report

ESF Exploratory Workshop on

Gene-Environment Developmental Models of Emotional Disorders: Bridging Human and Animal Research

Rome, Italy, 11 - 13 May 2007

Convened by:
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Executive Summary

While the second half of the twentieth century has been marked by a series of changes about the prevailing views of the role of genetic and environmental factors in the causation of mental disorders, there is now widely-spread consciousness that both the genetic and non-genetic ultimate determinants of behaviour and psychopathology need be considered in their reciprocity (Rutter et al., 2006). Such convergent view is now deemed fundamental for a better understanding of the causes of normal and abnormal behaviour, as well as for the prevention and therapy of mental disorders in the developmental years. Some of the most crucial insights in the field of behavioural/psychiatric genetics (Boomsma et al., 2002) can be summarized as follows: a) the liability which underlies several normal and abnormal behaviours is multifactorial in nature and continuous in distribution, with several genes of small -but significant- effect, and many environmental factors –each adding a small, but potentially relevant contribution - acting together to influence individaul variation along many behavioural phenotypes; b) for each of the genetic elements involved in a given mental disorders, the predisposing alleles are most likely common polymorphic -rather than rare and highly detrimental- variants of genes whose variation has been tolerated in human evolution; c) the causal pathway from the genetic and environmental ultimate causes to observed behaviour is best represented as a probabilistic, not deterministic, reaction surface (Gould & Gottesman, 2006).

Within this framework of reference, the gene-environment (G x E) interplay has become a central issue on the way towards a better understanding of psychopathology in the developmental years. Several different pieces of evidence have contributed to raise the interest in G x E, including the increasing appreciation of the importance of epigenetic mechanisms, the evidence of variation in heritability across different social strata, and several examples of gene-environment correlation (Kendler & Eaves 1986; Battaglia & Ogliari, 2005; Rutter et al., 2006). More recently, with the advent of the so-called genomic and post-genomic era (Plomin et al., 2003), the study of the influence of specified genes in specific environmental conditions has become possible, and animal models, with their opportunity of highly-controlled environmental conditions, and the availability of *ad hoc* inbred and outbred strains, have become a precious opportunity to streamline the study of G x E interaction. As such, animal models of human developmental psychopathology can constitute the fully experimental environment where to export paradigms of G x E interaction suggested by human semi-experimental or naturalistic studies. The rigorously controlled experimental conditions of the animal laboratory and the possibility of testing clearly, *a priori* specified, competing causal models is highly needed by researchers in human psychopathology (Troisi & D'amato, 2005). Conversely, indications of G x E interaction provided by animal models can kindle new hypotheses in human developmental psychopathology (Battaglia, 2002).

However, several researchers both on the 'human' and the 'animal' front share the view that across-fields' communication is often less than optimal. Investigators in human behavioural/psychiatric genetics, translational neuroscience, and in animal models have developed impressive methodologies, but somehow paradoxically, there seems to be only a modest osmosis of knowledge and ideas across these domains. For instance, researchers who work on animal models of anxiety often remain in the safe waters of a small set of laboratory behavioural paradigms: although these are highly replicable, they remain only modestly applicable to human specific clinical subtypes of anxiety. The possibility of applying to the animal some endophenotypes which have been validated in the human is also too often ignored. On the other hand, researchers in human developmental psychopathology often fail to fully appreciate the possibility of the highly-controlled experimental conditions offered by animal testing. Too often they complain about the inherent difficulties of 'studying the environment' while clear, 'a priori', falsifiable G x E hypotheses could be appropriately explored in the laboratory.

While technically highly sophisticated, the fields of behavioural genetics, of animal model studies of emotional disorders, and of translational clinical research in developmental psychopathology, are presently at risk of reciprocal divergence. This risk is unwanted and in the medium term it may not be sustainable under several points of view. An interdisciplinary approach is then needed. Points of contact among scholars working in these germane disciplines can be found in methodological improvements within the realm of experimental G x E interactions related to valid animals models, and in the implementation of endophenotypes which can be investigated simultaneously in animals and man, downstream of gene expression and upstream of clinical symptoms, that necessitate increased collaborations between clinical and bench scientists (Gould & Gottesman, 2006).

This Workshop was then conceived as explorative in its very nature: in that we sought to have scholars taking the risk of crossing the boundaries of their disciplines and putting their boldest ideas, hypotheses and expertise at the service of fellow researchers in other, related fields. Starting from a critical point of view towards their specific field of expertise, and openly addressing the points which are most needful for new vistas, they were called to evoke suggestions from fellow scientists from neighbouring areas.

One innovative aspect of the Workshop was that of having also clinician scientists in the panel of presenters and discussants, to address the distance currently separating animal models, genetic-epidemiological studies and clinical practice. One practical point of contact among related fields was identified in the availability of some endophenotypes which can simultaneously and interchangeably applied to animal models, genetic-epidemiological studies, and clinical practice in psychopathology (Gould & Gottesman, 2006). As such, this Workshop provided a rather unique and innovative occasion for a small group of researchers within the EC to freely interact on what are the difficulties in connecting human studies to animal research and vice-versa, on how they can reciprocally improve their work, and on how to expand on practical implications in mental health-related problems.

We think this Workshop made a significant step towards better (i.e., more up-to-date, clinically-relevant) models of G x E interaction to investigate the etiology of emotional disorders in development. The future development of animal models for psychiatric disorders will require a greater focus on validated endophenotypes, rather than on symptom-based models (Gould & Gottesman, 2006). This revision may in turn lead to better readouts, which can better translate pharmacogenomics into clinical practice.

The Workshop was thus aimed at supporting a cultural and technical effort which can be sustained only through a European-scale collaboration, as suggested by the variegated panel of international experts. It is in fact unrealistic that a single nation or even a small consortium of few nations can effectively address these issues successfully.

Beyond cultural advancements, the Workshop added potential for heralding collaborative efforts between participants which have already been primed, for initiating follow-up research activities and/or developing future collaborative actions among participants and within the EC.

Scientific Content of the Event

DAY 1

Stella Canna-Michaelidou (ESF Standing Committee for Life, Earth and Environmental Sciences)

Dr Michaelidou provided a presentation of the several initiatives currently being undertaken at the ESF Committee for Life, Earth and Environmental Sciences which can be of relevance to the attendees of this Workshop; in particular she provided useful information about forthcoming granting initiatives which could be seized by researchers in biomedicine and biology.

Ero Vasar (ESF Standing Committee for Medical Sciences)

Dr Vasar provided a brief reflection on the needs for more communication between human and animal researchers, the focus of the ESF workshop.

Thalia Eley:: *Gene-environment interplay: a human developmental perspective on emotional disorders*

Dr Eley presented a compelling review of how intermediate phenotypes and/or endophenotypes can effectively promote research in developmental anxiety disorders by showing how contemporary twin studies can gain better power to identify additive genetic effects by the adoption of such measures. Of special relevance, Dr Eley showed how the anxiety sensitivity index can improve the power of twin analyses once it ia adopted as an intermediate phenotype.

Alfonso Troisi: *Gene-environment interactions in the development of adult attachment styles*

Dr Troisi presented in a framework of gene-environment interplay, a set of new, unpublished data on the effects of different common identified functional polymorphisms upon human attachment styles in general population adult subjects. Differently from some studies which failed to provide a strong evidence in favor of genetic influence upon attachment styles in children, Dr Troisi was able to detect a small but significant effect in this adult population.

Ron De Kloet: *Stress hormones, Neurodevelopmental Setpoints and Susceptibility Pathways in the Brain*

Dr De Kloet presented a compelling review together with some new data of how stressful experiences in the animal (mouse) can affect different brain pathways and alter different behaviors depending on the time window when stress is applied. Particularly Dr De Kloet has shown dramatic functional, anatomic, and behavioral data concerning the consequences of time-locked early stressors on learning.

Lise Gutnecht *Neural Correlates of Epigenesis*

Dr Gutnecht presented an overview of how different common identified functional polymorphisms can influence a set of neurofunctional readouts in humans engaged in different cognitive tasks.

Katherine Belzung: *Epigenetic factors contributing to stress sensitivity:data from rodent studies*

Dr Belzung provided a review lecture focused on how classic anxiety tests in the rodent are likely affected by stress sensitivity, which can be ultimately ascribed to likely epigenetic mechanisms affecting genes' expression.

General Discussion: all presentations were followed by detailed discussion of the data and lively debate and interaction, as was the general discussion which put an end to the 1st day of the workshop.

DAY 2

Marco Battaglia: *Dissatisfaction with current phenotypes in developmental behavioural genetics of emotional disorders: reflections and proposals*

Dr Battaglia started by briefly reviewing the drawbacks of insufficient communication between human and animal researchers; then he presented new data on a large cohort of twins undergoing a CO2 provocation challenge and data on a new animal model of panic in collaboration with the laboratory of F D'Amato, suggesting that parallel studies of endophenotyuope sin animal and man can be fruitful.

Iftach Shaked *Cholinergic Checks and Balances for Mammalian Stress and Anxiety Reactions: from Mice to Men and Back*

Dr Shaked showed how stressful experiences can mediate neuronal plasticity by direct action upon the genetic expression of cholinergic receptors in the relative long-term, by the expressions of a readthrough variant of acetylcholinesterase, which is released in stressful conditions in the alternative to the synaptic variant, as a possible protection against neurodeterioration. Pros and cons of this system have been reviewed ion the light of anxiety proneness.

Ora Kofman *Emotional behaviour and learning in adults following exposure to cholinesterase inhibitors in the preweanling period*.

Dr Kofman showed how adults mice following exposure to cholinesterase inhibitors in the showed altered emotional behaviors (anxiety especially), and altered learning, and how functions could be rescued by acting on the cholinergic system .

Elias Eriksson: *The hypersensitivity to cabon dioxide as an endophenotype of human and animal anxiety*

Dr Eriksson showed how hypersensitivity to cabon dioxide can be employed as an endophenotype of human and animal anxiety, and based mainly on pharmacological probing, how this trait makes a valuable proxy to study anxiety in the animal .

Hanno Wurbel: *Effects of enriched environment on mouse behaviour*

Dr Wurbel provided a compelling review of how the lab environment has a tremendous impact on mouse behaviour and experiments. He stressed the importance of considering environmental variables when measuring genetic effects and the importance of more ecological settings.

Wiiliam Waldar: *Gene by environment interactions on multiple phenotypes in a large cohort of outbred mice*

Dr Valdar showed a novel approach to the complex picture of multiple phenotypes in outbred mice in presence of g x e interactions, with special reference to linkage strategies and in presence of genetic background effects.

Cornelius Gross: *Studying interactions between genes and rearing environment in the mouse*

Dr Gross provided compelling evidence of how the rearing environment in the mouse is a critical background against which to contrast genetic-driven responses, with particular attention to the serotonergic system and its modulatory activity on the amygdala.

Francesca D'Amato: *Non-genomic transmission of ecologically-relevant information: the role of the mother*

Dr D'Amato reviewed the importance of mother-pup interaction in the transmission of ecologically-relevant information with special attention to parallels to human anxiety disorders and to the modulation of expression of a host of genes that can influence emotional behaviour in animal and man.

General Discussion: all presentations were followed by detailed discussion of the data and lively debate and interaction, as was the general discussion at the end of thi second and last day of workshop.

Assessment of Results

Overall, the aim of promoting the interaction between researchers in human genetic epidemiology and researchers in the field of animal models has been fulfilled. During the discussions and interactions we witnessed a growing interest of researchers in one field for what people in the other field were doing, and what perhaps counts more, acknowledgment of several oversimplifications proper of each sub-field. In the endeavour to understand how genetic and environmental factors influence vulnerability to emotional disorders, with special attention to the developmental span of life, this workshop has had the merit of putting together persons who otherwise would have had limited possibility to interact.

Some of the participants are already engaged in exploring the possibility of applying to the animal some endophenotypes which have been validated in the human, and presenting preliminary data of this collaboration has been stimulating for the audience.

In general all participants provided positive comments about the usefulness of this workshop, and part of the general discussion was also aimed at how finding calls for conjunct applications of participants at the EC level (e.g., Eurocores programme).

Final Programme

Friday 11 May 2007

Morning	*Arrival*
15.00	**Opening time**
15.15-15.30	**Presentation of the European Science Foundation (ESF)** **Stella Canna-Michaelidou & Ero Vasar** (ESF Standing Committees for Life, Earth and Environmental Sciences, and Medicine)
15.30-16-00	**Thalia Eley (Iop London)**: *Gene-environment interplay: a human developmental perspective on emotional disorders*
16-10-16.40	**Alfonso Troisi (Tor Vergata Rome)**: *Gene-environment interactions in the development of adult attachment styles*
16.50-17.20	**Ron De Kloet (U of Amsterdam the Netehrlands)**: *Stress hormones, Neurodevelopmental Setpoints and Susceptibility Pathways in the Brain*
17.30-18.00	**Lise Gutnecht (Wurzburg U Germany)***Neural Correlates of Epigenesis*
18.10-18.40	**Katherine Belzung (U of Tours France)**: *Epigenetic factors contributing to stress sensitivity: data from rodent studies*
18.50-19.30	**General Discussion** followed by *Get Together cheese and wine party at workshop site*
20.30	*Dinner at Trattoria Trastevere*

Saturday 12 May 2007

09.00	**Opening time**
09.00-09.30	**Marco Battaglia (San Raffaele U Milan)**: *Dissatisfaction with current phenotypes in developmental behavioural genetics of emotional disorders: reflections and proposals.*
09.40-10.10	**Iftach Shaked (Weizman Inst Israel)**: *Cholinergic Checks and Balances for Mammalian Stress and Anxiety Reactions: from Mice to Men and Back*
10.20-10.50	**Ora Kofman (U of the Negev Israel)** (*Emotional behaviour and learning in adults following exposure to cholinesterase inhibitors in the preweanling period*.
11.00-11.30	**Elias Eriksson (Gotheborg U Sweden)**: *The hypersensitivity to cabon dioxide as an endophenotype of human and animal anxiety*
11.40-12.15	**General discussion**
12.15-13.15	*Lunch at workshop site*
14.00-14.30	**Hanno Wurbel (U of Zurich Switzerland)**: *Effects of enriched environment on mouse behavior*

14.40-15.10	**William Valdar (Wellcome Centre UK)**: *Gene by environment interactions on multiple phenotypes in a large cohort of outbred mice*
15.20-15.50	**Cornelius Gross (EMBL Monterotondo)**: *Studying interactions between genes and rearing environment in the mouse*
16.40-17.10	**Francesca D'Amato (CNR Rome)**: *Non-genomic transmission of ecologically-relevant information: the role of the mother*
16.00-16.30	*Coffee break at workshop site*
	Round Table addressing a planning of follow-up research activities and/or collaborative actions or other specific outputs; and **Conclusions**
20.30	*Dinner at Trattoria Pompiere*

Sunday 13 May 2007

Morning	*Departure*

List of Participants

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Statistical information on Participants

Repartition by country of work:

DE	2
FR	1
IL	3
IT	4
NL	1
SE	1
UK	2

Repartition by gender:

Male	7
Female	7